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The Total Syntheses of Ring-A Substituted Ergolines

Complies with University regulations and meets the standards of the Graduate School for originality and quality

For the degree of Doctor of Philosophy

Signed by the final examining committee:

David E Nichols, chair

Mark Cushman

Gary E. Lee

A. R. Buzzo

Approved by: [signature] June 25, 1998
Department Head Date

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THE TOTAL SYNTHESES OF

RING-A SUBSTITUTED ERGOLINES

A Thesis

Submitted to the Faculty

of

Purdue University

by

Sunkyung Lee

In Partial Fulfillment of the

Requirements for the degree

of

Doctor of Philosophy

August 1998

To...

my mom and dad

my husband, Hasik

and my sons, Kyusup and Joongsup

ACKNOWLEDGMENTS

I would like to express my sincere thanks to my major professor, Dr. David E. Nichols for his encouragement, guidance, patience, and thoughtful consideration during my research. Dr. Nichols always gave me good advice whenever I asked and guided me how to solve the problems that arose during the syntheses. I would like to thank the members of my committee, Dr. Mark S. Cushman, Dr. Gary E. Isom, and Dr. Stephen R. Byrn.

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LIST OF ABBREVIATIONS

Ar	Aromatic
brine	saturated aqueous sodium chloride
BHT	2,6-di-*tert*-butyl4-hydroxytoluene
°C	degrees centigrade
CIMS	chemical ionization mass spectroscopy
conc	concentrated
DA	dopaminergic
dec	decomposition
DIBAL	diisobutylaluminum hydride
DME	ethylene glycol dimethylether
DMF	dimethylformamide
DMFDMA	dimethylformamide-*N,N*-dimethylacetal
DMSO	dimethylsulfoxide
DMT	*N,N*-dimethyltryptamine
DOM	1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane
eq	equivalent(s)
FABMS	fast atom bombardment mass spectroscopy

g	gram(s)
h	hour(s)
HMPT	hexamethylphosphorous triamide
HR	high resolution
5-HT	5-hydroxytryptamine, serotonin
ip	intraperitoneal
LAH	lithium aluminum hydride
LSD	lysergic acid diethylamide
M	molar
μg	microgram(s)
μL	microliter(s)
mg	milligram(s)
min	milliliter(s)
mmol	millimole(s)
mp	melting point
m/e	mass to charge ratio
N	normal
nM	nanomolar
NMR	nuclear magnetic resonance spectrometry
$pdCl_2(dppf)$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium
PPA	polyphosphoric acid
TFA	trifluoroacetic acid

TLC	thin layer chromatography
TMSI	trimethylsilyl iodide

ABSTRACT

Lee, Sunkyung. Ph.D., Purdue University, August, 1998. The Total Syntheses of Ring-A Substituted Ergolines. Major Professor: David E. Nichols.

Three types of ergolines, having a substituent in ring A were designed and their total syntheses were attempted. *N*-substituted 12-methoxyergolines were synthesized as potential serotonergic agents to test the hypothesis of bioisosterism between the C8 carbonyl oxygen of LSD and an *ortho* oxygen or a 5-oxygen atom in hallucinogenic phenethylamines and tryptamines, respectively.

To investigate the enhanced dopaminergic effect of 13-hydroxylation of ergolines, 2-hydroxybenzergolines and 13-hydroxyergoline were designed. A variety of approaches were examined to effect the construction of these targets. A classical approach involving the construction of 4-keto-7-methoxybenz[*cd*]indole as a synthon was unsuccessful. Several different attempts to prepare this tricyclic ketone all failed, apparently due to the decreased reactivity of the indole-4-position that results from the presence of the methoxy group at the 6-position of indole in the necessary precursors to the tricyclic ketone.

Alternative synthetic approaches involved Suzuki cross-coupling of 6-methoxyindole-4-boronic acid with either a 4-substituted isoquinoline or 3-substituted pyridine precursor. Although the coupling reactions proceeded well, intramolecular ring closure reactions to construct ring C generally failed. Of particular note, however, is

potential for a Hammick reaction to effect this transformation, and promising preliminary results in this thesis work suggesting that future efforts employing this approach may be fruitful. An additional promising route involved the Minisci reaction, which in this work was successfully employed to produce a 13-methoxy-4-oxoergoline.

INTRODUCTION

Ergot Alkaloids

Officially, ergot comprises the sclerotium, which is the resting stage of the fungus *Claviceps purpurea.* The ergot alkaloids constitute the largest known group of nitrogenous fungal metabolites. Pre-Christian allusions to its effects have been recorded, and it was identified in 1696 as the causative agent of the dreaded medieval gangrenous scourge, St. Anthony's Fire. The therapeutic importance of ergot was first recognized during the middle ages. Its capacity to induce uterine contraction was recorded as early as 1582, and crude preparations were introduced into orthodox medicine early in the nineteenth century.[1] During the middle twentieth century, isolation and structural elucidation of pure active principles of ergot were accomplished. Arthur Stoll[2] played a dominant roll, directing the isolation of no less than six related bases, all of which have been shown to be amides of the same key substance, lysergic acid,[3] having a unique tetracyclic ring system named "ergoline".

Ergot alkaloids, because of their remarkable biological activities, represent an important group of indole alkaloids, and several of them have found useful medicinal applications. At the same time, LSD (Figure 1), also a semisynthetic analogue of this group of indole alkaloids, is one of the most potent hallucinogens known.

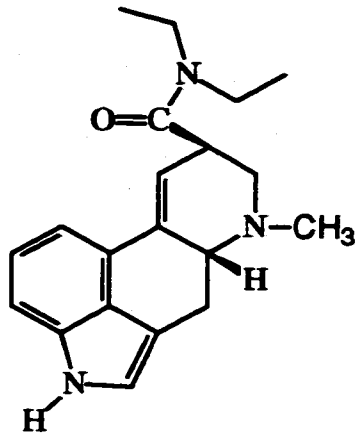


Figure 1. Structure of *d*-LSD

Classification of Ergot Alkaloids

Judging from structural features and consideration of biosynthetic pathways of compounds so far isolated, ergot alkaloids can be classified into the following major groups[4] (Figure 2): (1) ergolines, (2) 8-ergolenes (8,9-didehydroergolines), (3) 9-ergolenes (9,10-didehydroergolines), (4) secoergolines, and (5) deformed ergot alkaloids. Further, these classes are subdivided according to substituents, particularly at the 8 position, for example, methyl, hydroxymethyl, formyl, or carboxyl. The most common derivatives are the 9-ergolenes with an 8-carboxyl group, which are derived from lysergic acid. The 8-carboxy-substituted 9-ergolenes exist in nature mainly as the amide form coupled with an amino acid or peptide. The use of ergot alkaloids in medicine is centered on this type of lysergic acid peptide amide.

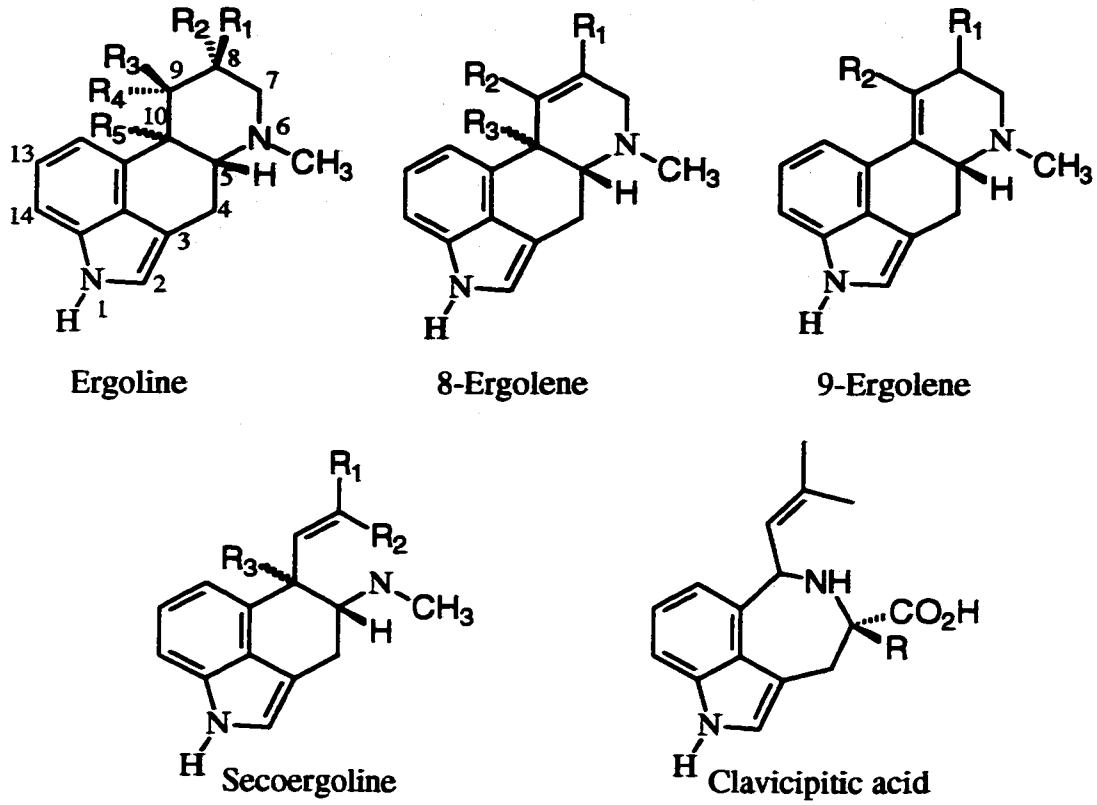


Figure 2. Classification of ergot alkaloids

Total Synthesis of Ergot Alkaloids

Widespread interest in the synthesis of lysergic acid was stimulated even before the structural issues were resolved in 1949.[2] The synthesis of dihydrolysergic acid by Uhle and Jacobs[5] was the first major synthetic accomplishment. The first total synthesis of the racemate of lysergic acid was achieved in 1954 by the collaboration of a group of Eli Lilly chemists led by E. C. Kornfeld.[6]

Kornfeld and co-workers used an indoline derivative as a starting material. In order to promote cyclization of substituents at the 3-position into the 4-position, the indole ring was converted to the corresponding indoline derivative (Figure 3). This cyclization to

form ring C by Friedel-Crafts acylation has been the most crucial step for the supply of a large quantity of starting material that is indispensable for the subsequent lengthy synthesis. When indoles were used in this reaction, various restrictions and limitations arose owing to instability of the skeleton. Several tricyclic derivatives were prepared by later researchers, including the β-tetralone,[7,8] the unsaturated aldehyde,[9] and the unsaturated cyanide,[10] thus bringing about the success of the total synthesis.

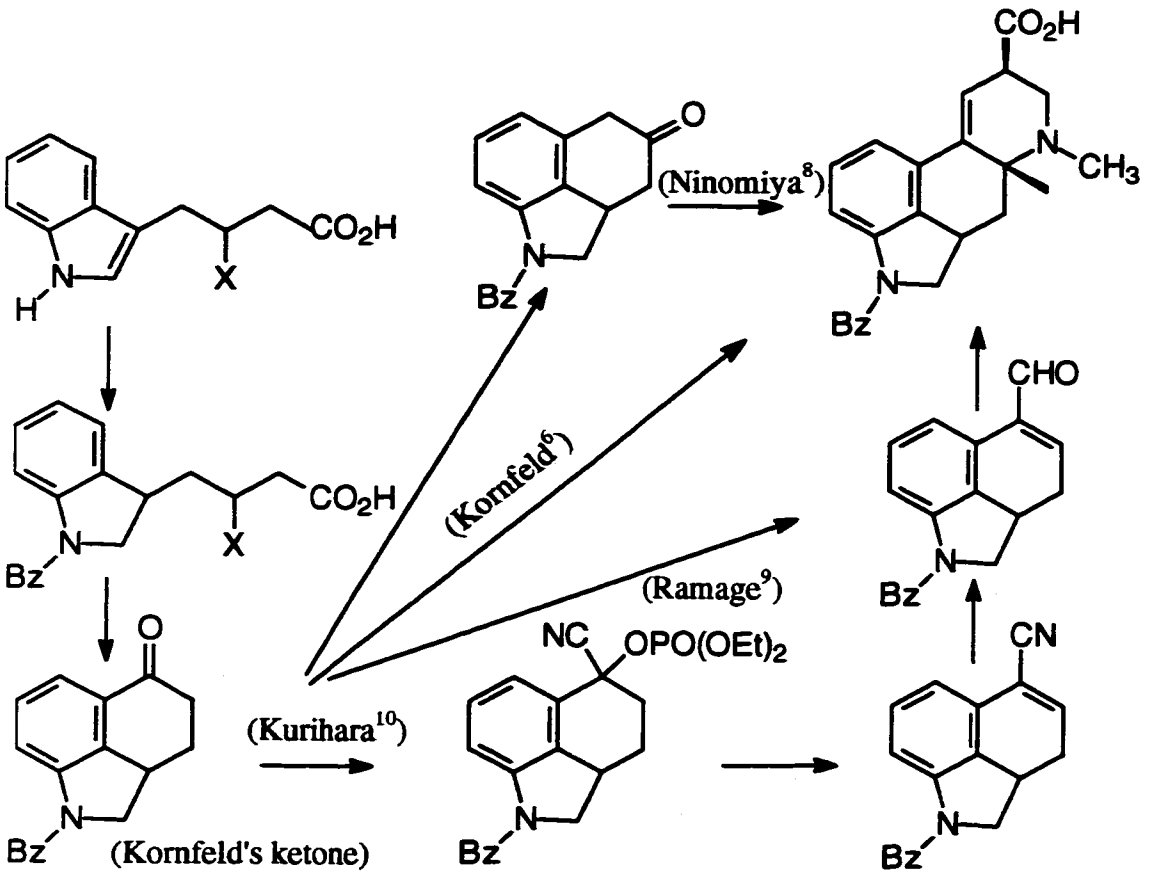


Figure 3. Synthesis of ergolines from indoline derivatives

Uhle reported[11] the intramolecular condensation of the diacid obtained from 4-cyanoindole to give "Uhle's ketone" (Figure 4). The first synthesis of ergoline beginning with an indole derivative was carried out with Uhle's ketone but failed to achieve the goal.[12] Later, newer synthetic routes starting with indole derivatives were developed, including the synthesis of (±)-lysergic acid *via* a route involving Diels-Alder reaction by Oppolzer's group,[13] Lewis acid-catalyzed synthesis of (±)-agroclavine I by Kozikowski's group,[14] and the synthesis of (±)-lysergene and LSD using cocyclization of 4-ethynyl-3-indoleacetonitriles with alkynes in the presence of $CpCo(CO)_2$ by Vollhardt's group.[15] All the syntheses of alkaloids beginning with indole derivatives have utilized the intramolecular cyclization of two substituents at the 3 and 4 positions.

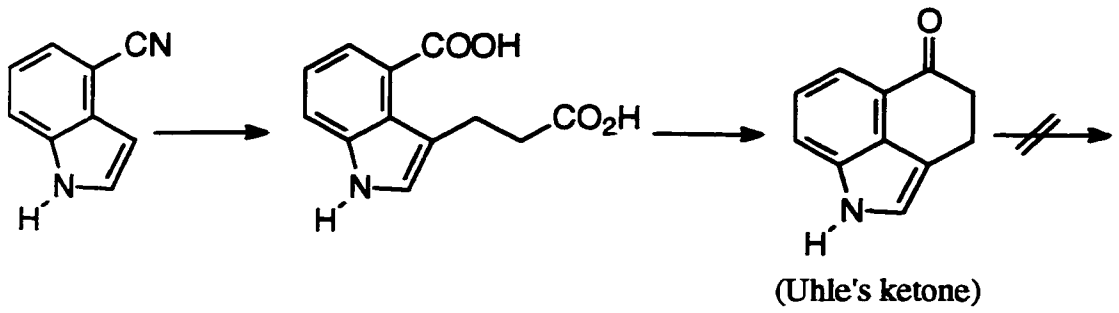


Figure 4. Synthesis of Uhle's ketone[11]

Synthesis of Skeletons of Ergolines

Syntheses of the skeletal structures of ergolines are divided according to the final bond formation reaction. There have been no reports of synthesis of ergoline-type skeletons with 3,4 or 7,8 bond formation as the last step.

Synthesis with 1,2 Bond Formation as the last step

Nitration of benzo[*f*]quinoline-6-carboxylates has been extensively studied with the aim of forming the 1,2 bond as the last step in synthesis.[16] This approach was seriously hampered by difficulty in hydrogenating rings C and D (Figure 5).

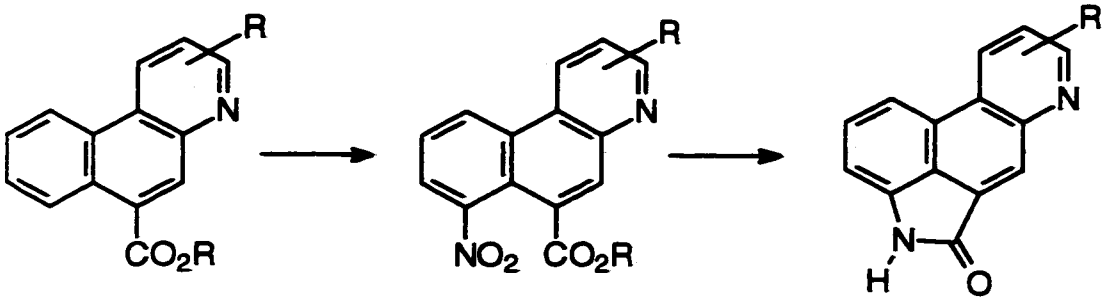


Figure 5. Synthesis with 1,2 bond formation as the last step.[16]

Synthesis with 2,3 Bond Formation as the Last Step

Haeflinger *et al.*[17] synthesized dihydrolysergic acid and its 14-substituted derivatives by formation of the indole ring as the last step using a nitrobenzo[*f*]quinoline, which was converted to the corresponding isonitrile (Figure 6).

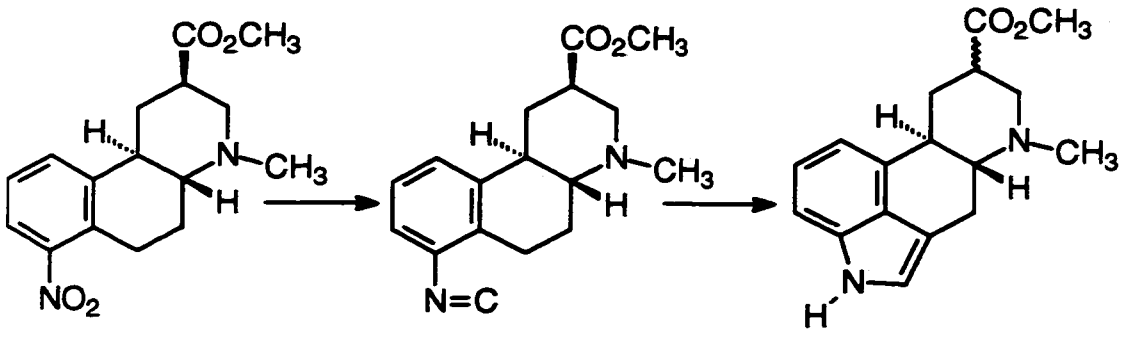


Figure 6. Synthesis with 2,3 bond formation as the last step.[17]

Synthesis with 4,5 Bond Formation as the last step

Somei *et al.*[18] developed a new and useful method of introducing various substituents at the 4 position by using (3-formylindol-4-yl) thallium bis(trifluoroborate), thus providing the possibility of formation of the alkaloid skeleton by cyclization of two substituents at the 3 and 4 positions (Figure 7). Although they did not apply the method to total synthetic work, they discovered new applications of organotin compounds for the introduction of substituents at the 4 position (tin-thall reaction) and another application of organoborane compounds for the boronation-thallation reaction.[19]

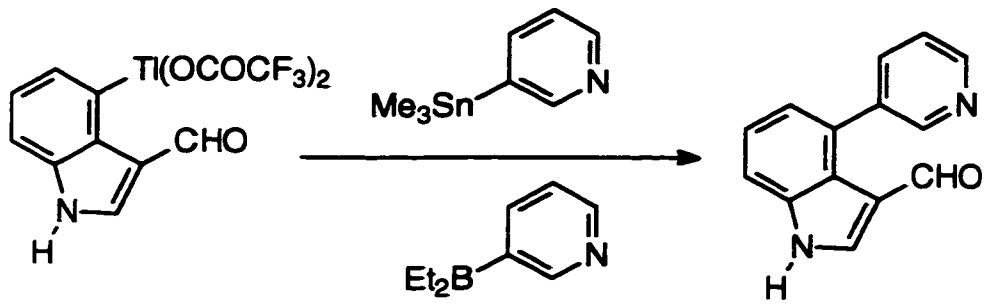


Figure 7. Synthesis with 4,5 bond formation as the last step.[18, 19]

Synthesis with 5,10 Bond formation as the Last step

Oppolzer *et al.*[13] succeeded in constructing the ergoline skeleton by applying the Diels-Alder reaction for formation of the 5,10 bond concomitantly with formation of the 6,7 bond. The reaction sequence was extended to the total synthesis of (±)-lysergic acid.

On the other hand, Hegedus *et al.*[20] investigated the Diels-Alder reaction of the 3,4-disubstituted indole derivative but did not achieve fruitful results (Figure 8).

The ergoline ring structure *via* an A,B → C,D ring assembly has been constructed, relying on the η^5-cyclopentadienylcobalt-catalyzed cocyclization of α,ω-alkynenitriles with alkynes to form 6,7, 8,9, and 5,10 bonds concomitantly by Vollhardt's group (Figure 8).[15] The cyclized compounds were transformed into racemic lysergene and LSD, respectively.

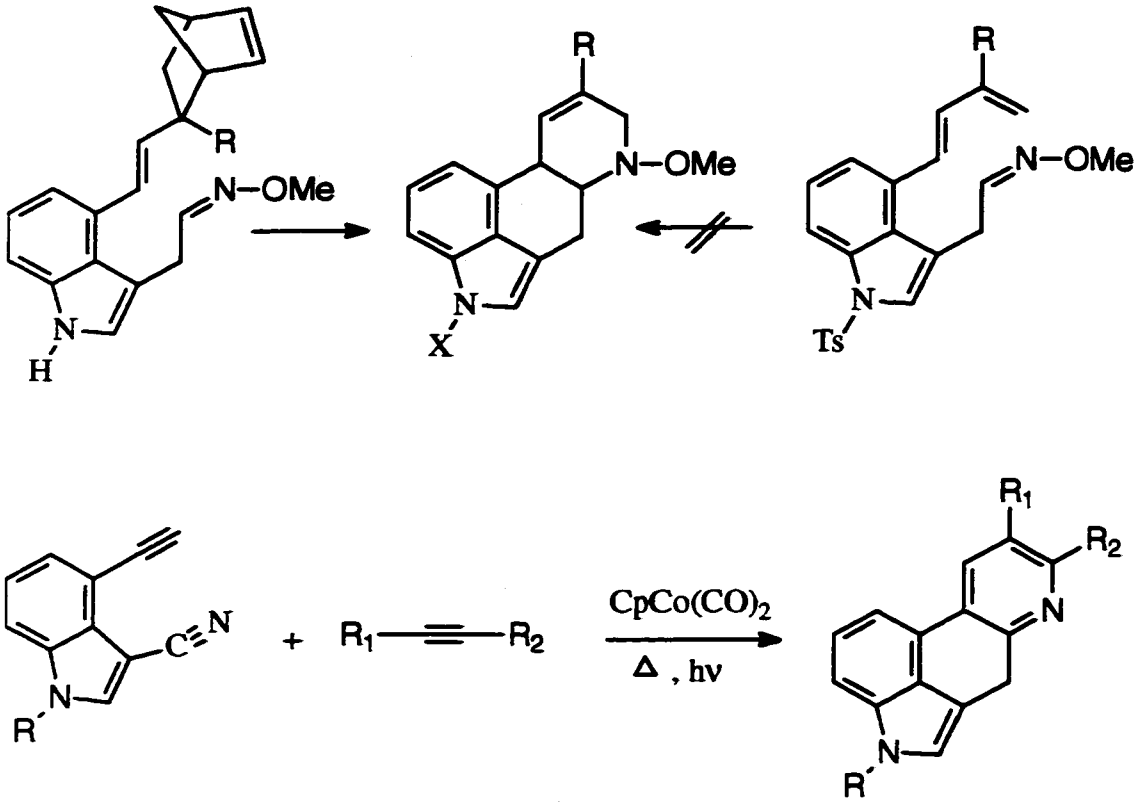


Figure 8. Synthesis with 5,10 bond formation as the last step.[13, 15, 20]

Synthesis with 10,11 Bond Formation as the Last Step

Several investigations have been carried out on application of the Pschorr reaction to 10,11 bond formation but without promising results.[21] Julia *et al.*[22] applied the benzyne reaction to 10,11 bond formation and further extended it to the total synthesis of (±)-lysergic acid (Figure 9).

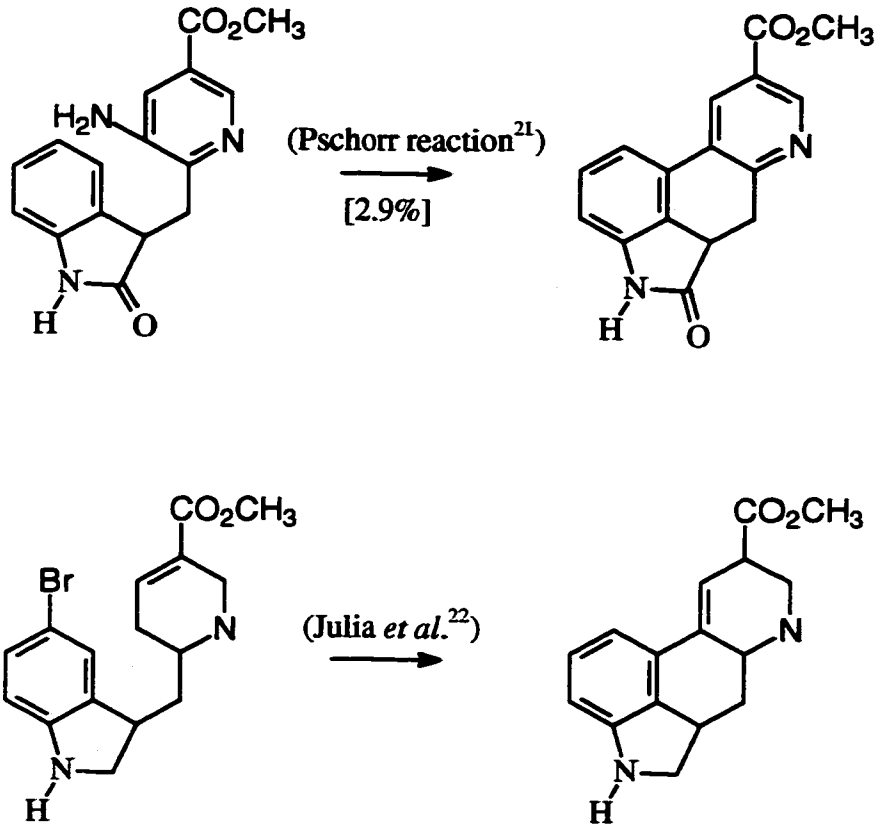


Figure 9. Synthesis with 10,11 bond formation as the last step

Synthesis with 5,6 Bond formation as the last step

In 1976, Ramage and co-workers succeeded in the total synthesis of (±)-lysergic acid *via* a route involving 5,6 bond formation as the last step (Figure 10).[9] The methodology consists of intramolecular Michael addition of an amino group to an unsaturated ester. A reaction analogous to the above Michael reaction was applied by Kurihara *et al.*[10] and by Cacchi *et al.*,[23] who independently succeeded in the total synthesis of (±)-lysergic acid.

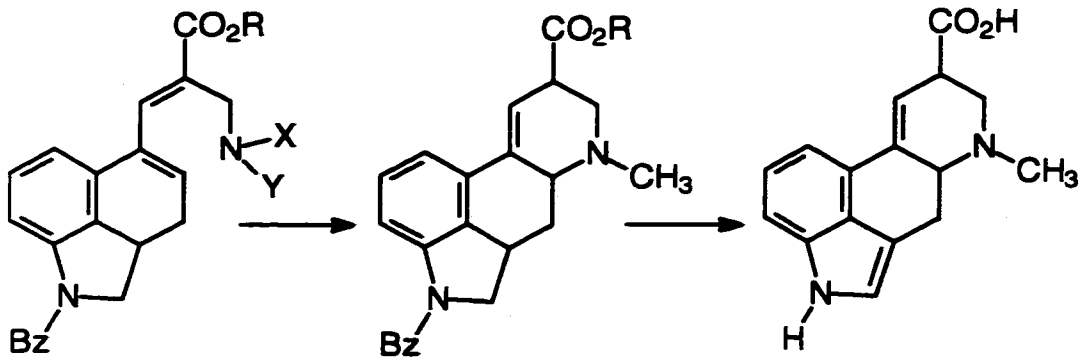


Figure 10. Synthesis with 5,6 bond formation as the last step[9]

Synthesis with 6,7 Bond Formation as the Last Step

All syntheses of ergoline skeletons by conversion of the ring system from 6,7-secoergoline skeletons involved 6,7 bond formation as the last step (Figure 11). Such an approach is exemplified by the synthesis of (±)-costaclavine by Oppolzer *et al.*,[24] (±)-agroclavine I by both Somei's group[25] and Kozikowski's group,[14] and (±)-dihydrosecoclavine by Natsume *et al.*[26]

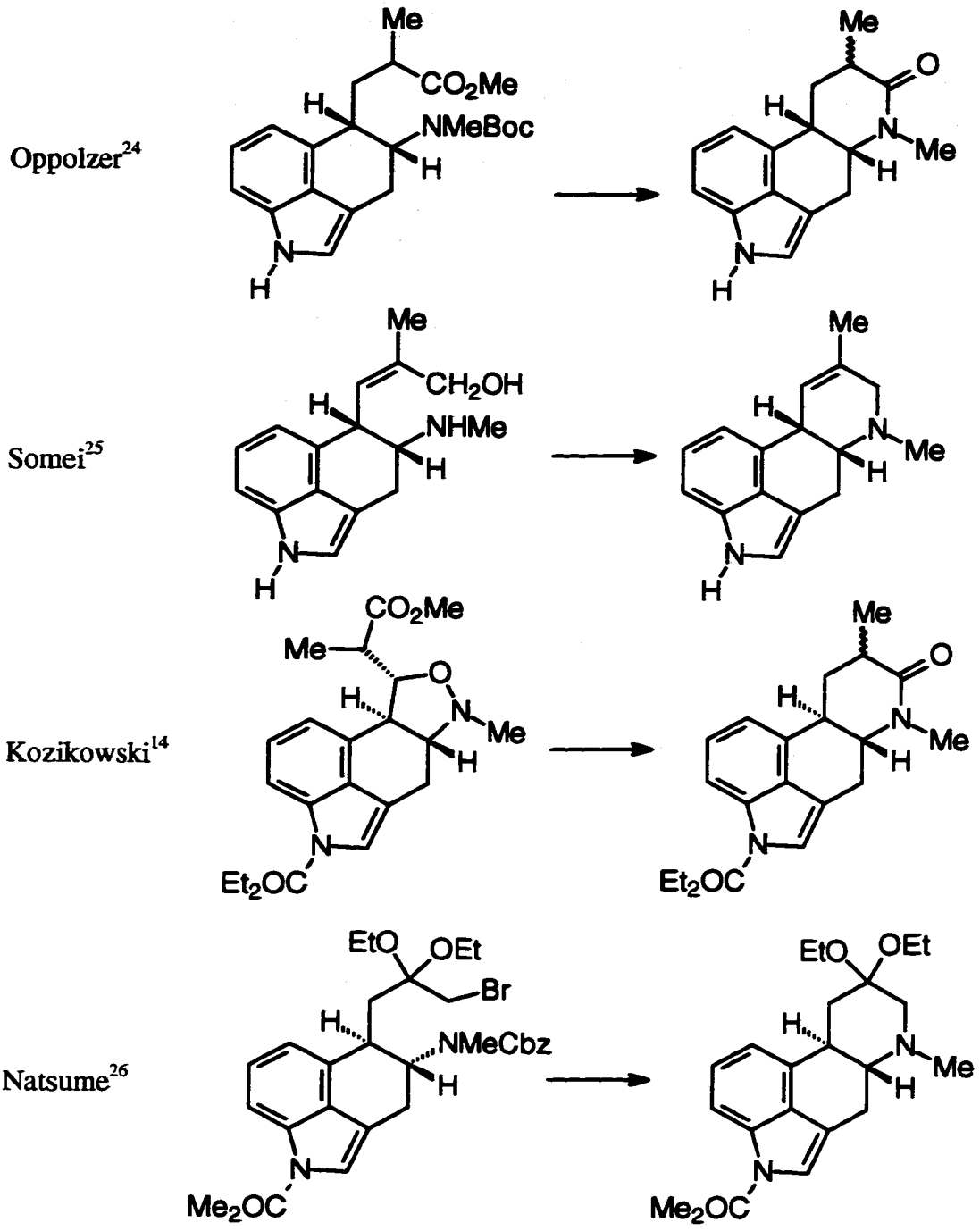


Figure 11. Synthesis with 6,7 bond formation as the last step

Synthesis with 9,10 Bond Formation as the Last Step

The first synthesis involving 9,10 bond formation as the crucial step was the first total synthesis of (±)-lysergic acid by Kornfeld and co-workwers (Figure 12A).[6] Ninomiya *et al.*[8] investigated photocyclization of enamides involving 9,10 bond formation as the crucial step (Figure 12B). Cassady and co-workers[27] exploited the high reactivity of the β-tetralone in the synthesis of the ergoline structure by forming both 9,10 and 6,7 bonds in one pot, as exemplified by the synthesis of (±)-dihydrolysergic acids (Figure 12C).

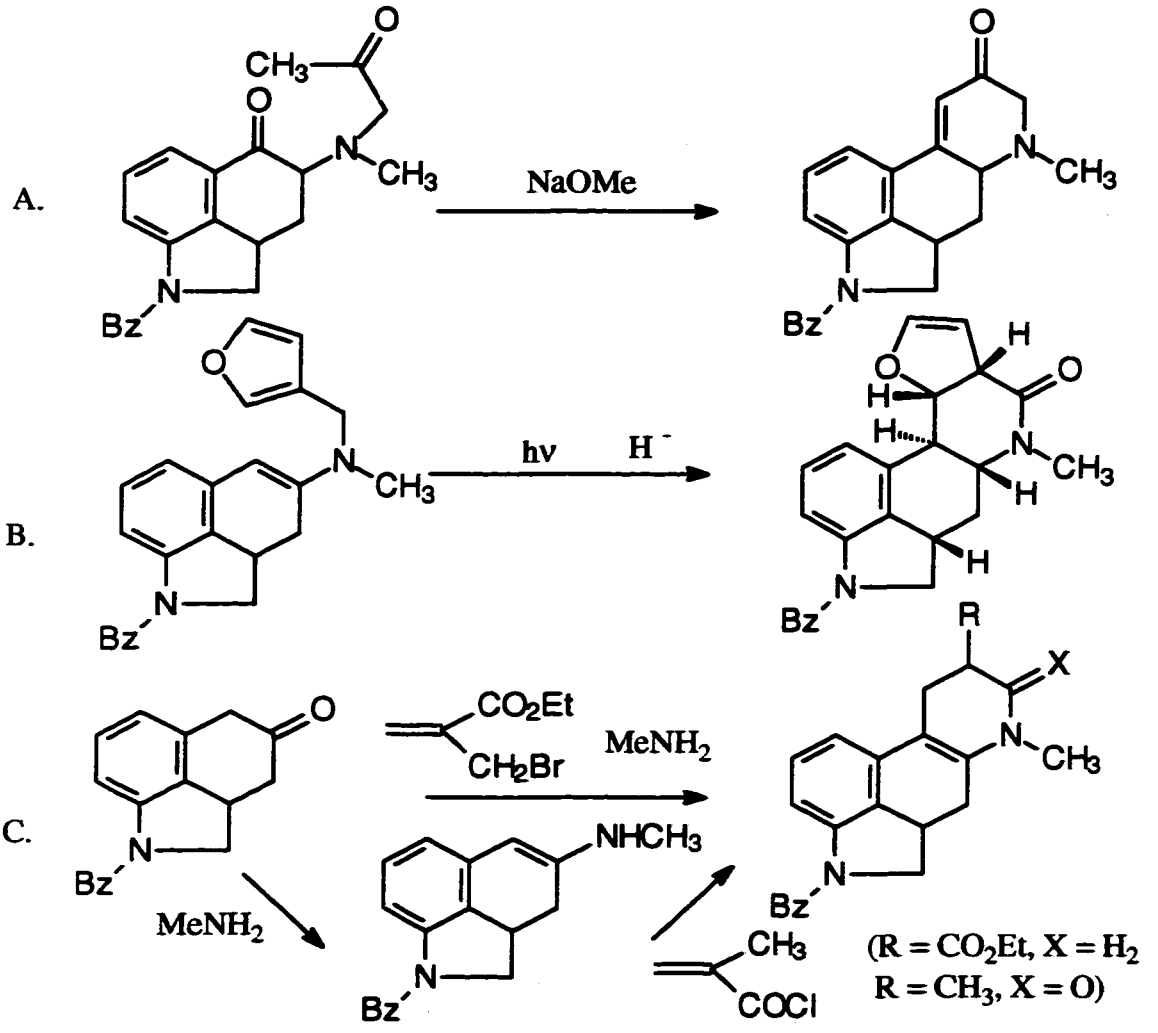


Figure 12. Synthesis with 9,10 bond formation as the last step[6,8,27]

In addition, synthetic studies using "Uhle's ketone" included 9,10 bond formation as the final step. However, all attempts to synthesize ergot alkaloids using derivatives of Uhle's ketone were unsuccessful. Bowman[28] also investigated the use of compounds prepared from Uhle's ketone in a synthetic study of ergot alkaloids but failed to reach the goal.

Synthesis of Modified Alkaloids

Extensive efforts to develop novel classes of physiologically active derivatives of ergot alkaloids have focused on structural modification of natural ergot alkaloids, particularly epimerization at the 8-position, substitution on nitrogen at the 6-position, carbon at the 2-position, and the indole nitrogen at the 1-position (Figure 13). But there are a few examples for the substitution of benzenoid ring A.

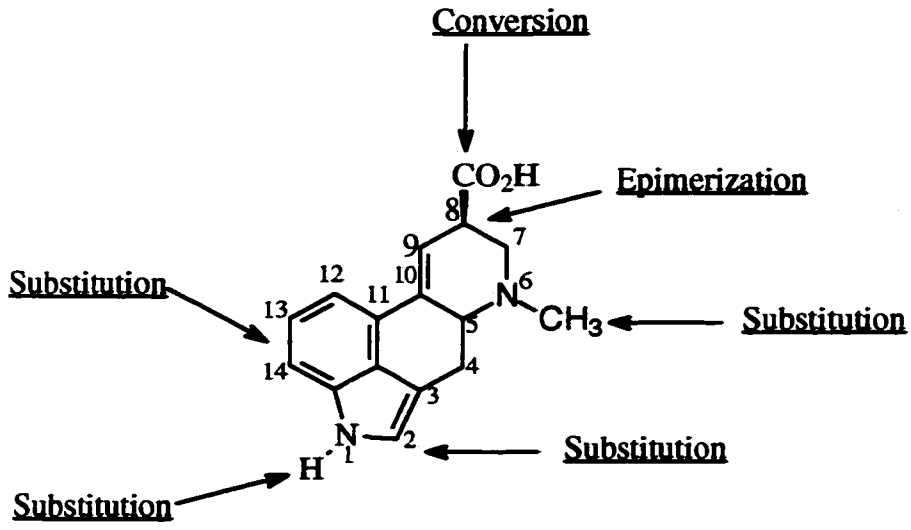


Figure 13. Approaches to structural modification of natural ergot alkaloids.

The Eli Lilly group[29] has achieved introduction of a 13-substituent into a 2-methylthioergoline derivative by bromination using pyridinium bromide perbromide followed by displacement of bromine using sodium methoxide in methanol/DMF in the presence of cuprous iodide (Figure 14). Demethylation to the 13-hydroxy derivative has been achieved using ethanethiol and $AlCl_3$ in CH_2Cl_2. This compound was suggested to be a dopamine partial agonist.

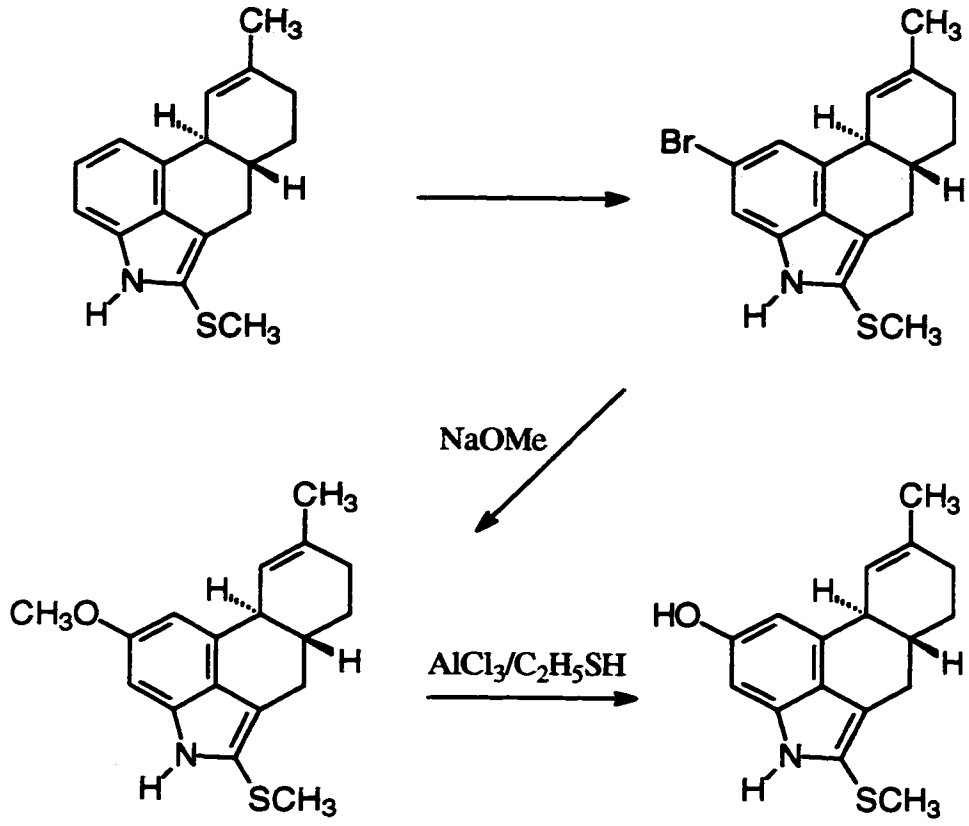


Figure 14. Introduction of a 13-hydroxy substituent[29]

The catalytic reduction at C(2,3) in the presence of fluoroboric acid of 1,6-dimethyl-8β-aminomethyl-10α-ergoline followed by acylation afforded a new series of highly active antiserotonin agents (Figure 15).[30] The 2,3-dihydro compounds have been used also as

intermediates for the synthesis of 12-hydroxyergolines. The presence of a hydroxyl at C12 was of interest in the search for active anti-serotonin agents because of the obvious similarity of this substitution to that of 5-hydroxytryptamine. It does actually appear that 12-hydroxy compounds are endowed with an extraordinarily high antiserotonin activity both *in vitro* and *in vivo*.[31]

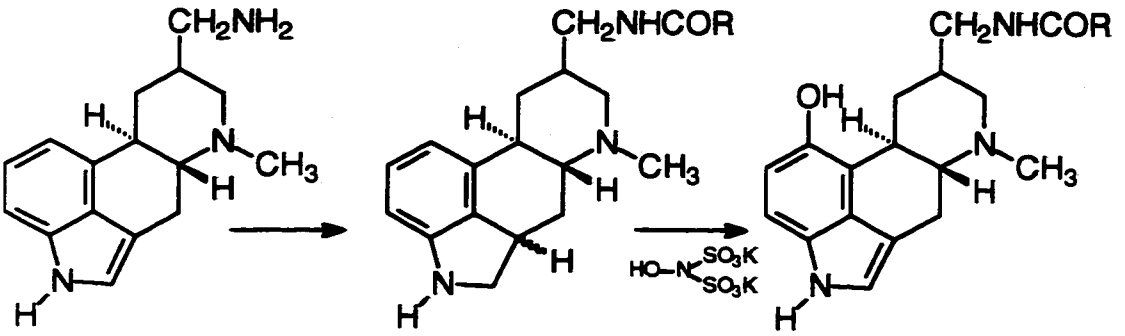


Figure 15. Introduction of a 12-hydroxy substituent[30]

Pharmacological Properties of Ergot Alkaloids

Ergoline derivatives exhibit complex pharmacological effects. Many ergot alkaloids and derivatives have been reported to produce the following principal effects, among others: uterotonic action, increase or decrease in blood pressure, induction of hypothermia and emesis, and control of the secretion of pituitary hormones.[32] The effects are mainly responses mediated by direct interaction with various neurotransmitter systems, such as the noradrenergic-, serotonergic-, and dopaminergic-systems. Perhaps no other group of natural products exhibits such a wide spectrum of biological action. Recently, attention has centered on the development of compounds with more selectivity rather than

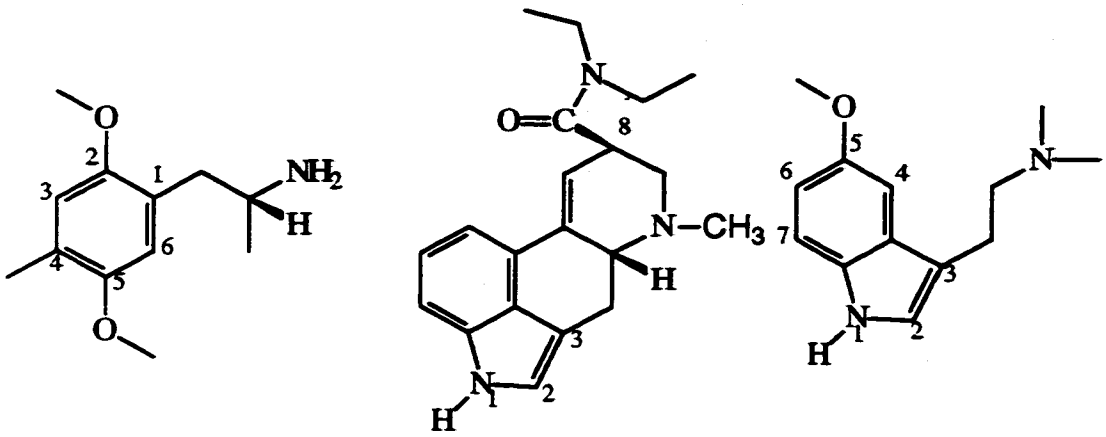
compounds with higher potency and some of these have been used to treat a number of clinical conditions. Our interests are especially focused on serotonergic and dopaminergic activities.

Effects of Ergolines on Serotonin Receptors

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter with numerous physiological functions in the central and peripheral nervous systems. Central serotonin binding sites were initially labeled in 1974 with [^{3}H]-LSD. However, it was soon shown that binding characteristics of [^{3}H]-serotonin and [^{3}H]-LSD were not identical. Thus, the high-affinity serotonin binding site was called the 5-HT_1 site, and it was suggested that LSD could bind not only to the 5-HT_1 site but also to another site, called the 5-HT_2 site. These sites are now further divided into several subtypes.[33] Therefore, finding a compound that binds specifically to a single class of active site would be instrumental to the elucidation of the *in vivo* role of serotonin, that is, the role and mode of action of serotonin at that particular receptor site. Many groups have researched along this line to uncover the relationship between serotonin receptor sites and ergot alkaloid pharmacology.[34,35]

Because LSD has high affinity for the serotonin 5-HT_2 receptor, as well as a number of other G-protein coupled receptors, it has generally been assumed to represent a rigid, tetracyclic analog of both the phenethylamine and tryptamine classes of hallucinogens (Figure 16).[35] If all three classes of hallucinogens bind to the receptor in a similar manner, the 5-methoxyl oxygen of DOM could serve as a bioisostere for the indole N1 nitrogen

atoms of LSD and tryptamine. Likewise, the phenethylamine O2 and tryptamine O5 atoms could be bioisosteric hydrogen bond acceptors that may also interact with the same receptor residue as the carbonyl oxygen of LSD. 12-Methoxyergoline compounds lacking a carbonyl oxygen at C8 will be valuable to test that hypothesis.



(R)-DOM *d*-LSD 5-methoxy DMT

Figure 16. Three classes of serotonergic compounds.

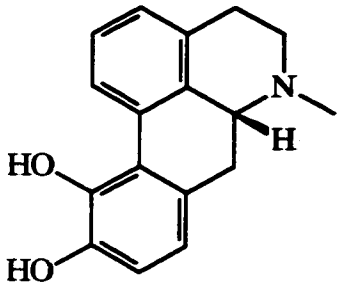
Effects of Ergolines on Dopamine Receptors

Ergoline derivatives exert dopaminergic (DA) agonist activity in the central and peripheral nervous systems.[32] Up to now, various correlations have been proposed between the ergoline derivatives and DA analogues in order to delineate the "dopaminergic portion" of the ergoline skeleton that confers DA activity upon the molecule. The correspondence of the indole NH and *m*-OH of the dopamine fragment has been proposed.[36] Nichols[37] originally proposed that the pyrroleethylamine moiety of ergots confers DA properties to this class of compound. All available data indicate that it

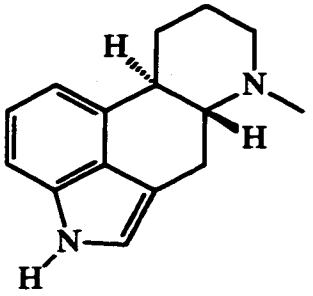
is the phenethylamine or the 2-aminotetralin moiety, which confers the high, central DA properties to apomorphine.

Compound CY 208-243,[38] which has a "benzergoline" structure has been shown to be a selective dopamine D_1 agonist (Figure 17). It has been postulated[39] that D_1 receptor affinity and intrinsic activity are favored by derivatives which combine a catechol and a secondary amine in a *trans*-β-rotametric dopamine structure and which rigidly maintain a second phenyl ring, attached at the 2-position of the ethylamine side chain, in an arrangement nearly coplanar with the catechol ring.

Nonselective

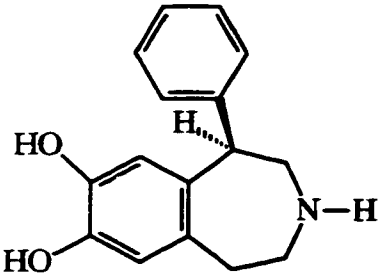


Apomorphine



Ergoline

Selective



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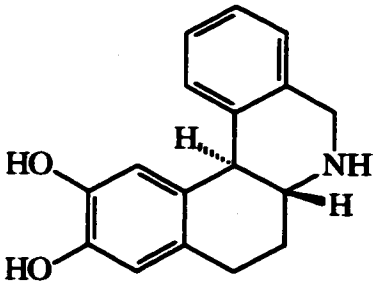
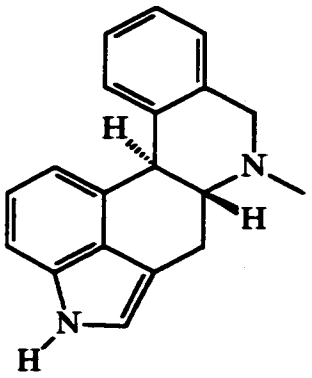


Dihydrexidine

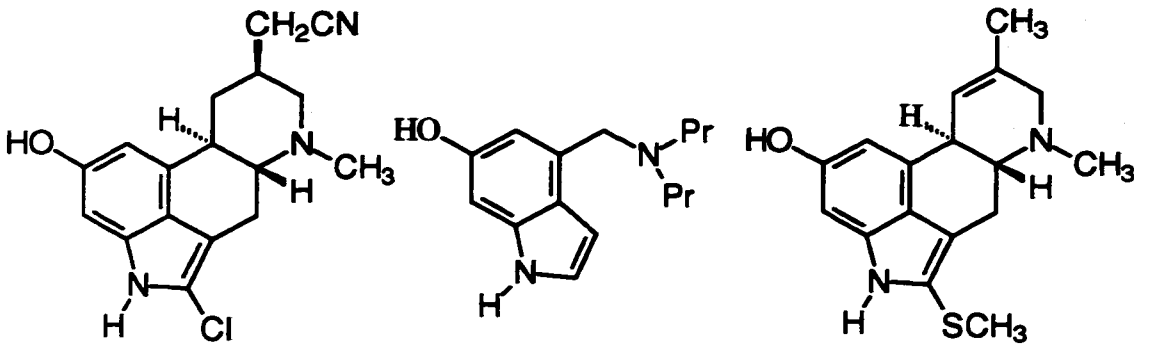


CY 208-243

Figure 17. D_1 Receptor activating compounds.

It was demonstrated more than two decades ago that a major route of metabolism for simple indole and tryptamines is hydroxylation at the indole 6-position.[40] For example, the ergoline lergotrile is a centrally acting dopaminergic compound.[41] Moreover, lergotrile is known to be hydroxylated *in vivo* at position 13, to give a molecule which is even more potent than lergotrile itself (Figure 18).[42] Using an *in vitro* assay to measure prolactin release from anterior pituitary, an effect mediated by dopamine D_2 receptors, 100 nM lergotrile gave 55% prolactin inhibition, while 13-hydroxylergotrile gave the same percentage inhibition at only 1.1 nM, being nearly 100 time more potent than lergotrile.[42] It has also been shown that 13-hydroxy-LSD is a major metabolite of LSD. As a further example, Cannon *et al.*[43] first showed that the 6-hydroxy derivative of 4-(*N,N*-dipropylaminoethyl)indole was at least ten-fold more potent than its nonhydroxylated parent. In an *in vivo* cat cardioaccelerator nerve preparation where the effects are mediated by dopamine D_2-type receptors, 6-hydroxy-4-(dipropylaminoethyl)indole was at least ten-fold more potent than its nonhydroxy compound. The 13-hydroxylated metabolite of the 2-methylthio compound (Figure 15) has also been identified as a metabolite in the rat, as is the case for LSD and lergotrile. Although the 13-hydroxylated compound showed a very similar affinity for the dopamine receptor to that of the parent 2-methylthio derivative (IC_{50} in [^{3}H]spiperone binding = 0.32 ± 0.11 μM), it was less active at blocking a conditioned avoidance response or producing catalepsy in the rat. It was explained that this compound was a partial agonist, as indicated by its ability to decrease serum prolactin (50% decrease at 1.0 mg/Kg ip), while the nonhydroxylated parent was an antagonist. Kocjan *et al.*[44] reported the molecular superimposition of

13-hydroxyergoline and apomorphine, which was obtained by matching their molecular electrostatic potential (MEP) patterns surrounding the aromatic moieties with respect to the coincident aliphatic N atoms. Therefore, hydroxylation at this position of the indole nucleus appears to have greatly enhanced the agonist properties of tryptamines and ergolines.



13-Hydroxy lergotrile

6-Hydroxy4-[(2-di-n-propylaminoethyl)]indole

8,9-Didehydro-6,8-dimethyl-13-hydroxy-2-(methylthio)-ergoline

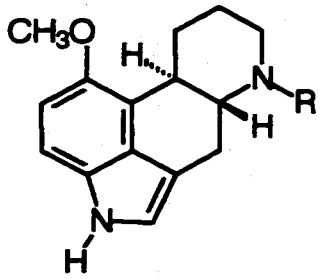
Figure 18. Compounds hydroxylated at the indole 6-position.

RATIONALE

Because of the remarkable physiological activity and structural variety of the ergot alkaloids, this class of compounds has been a continuing target on which to test the utility of novel synthetic methodology. However, there are not many examples for the synthesis of the ergolines which have a ring A substitution pattern. Only a few compounds with a substituent in ring A have been prepared by modification of the readily available ergot alkaloids themselves. This study presents several approaches to the synthesis of the three types of ergolines having a ring A substituent, which are expected to be valuable for pharmacological studies.

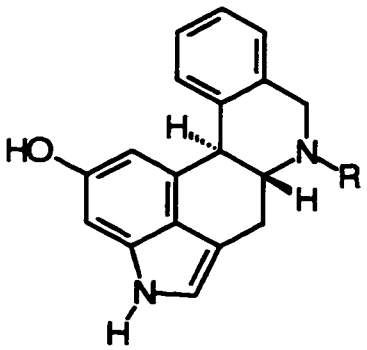
N-Substituted 12-methoxyergolines **1**, **2**, and **3** were synthesized as potential serotonergic agents to test the hypothesis[35] of bioisosterism between the C8 carbonyl oxygen of LSD and a phenethylamine O2 or a tryptamine O5 atom.

Enhanced dopaminergic activity of *in vivo* 13-hydroxylated metabolites of certain ergolines has been reported.[30,41] To examine related structures for similar pharmacology, 2-hydroxybenzergolines **4**, **5**, and **6**, and *N*-methyl-9,10-didehydro-13-hydroxyergoline **7** were designed and their total syntheses were attempted *via* several synthetic strategies.



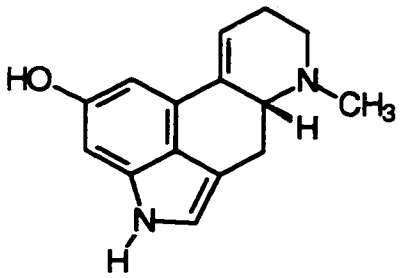
12-Methoxyergolines

R = -H **1**
-Me **2**
-Pr **3**



2-Hydroxybenzergolines

R = -H **4**
-Me **5**
-Pr **6**



9,10-didehydro-6-methyl-
13-hydroxylergoline

7

Figure 19. Target molecules

RESULTS AND DISCUSSION

12-Methoxyergolines

The retrosynthetic scheme for the preparation of 12-methoxyergolines **1**, **2**, and **3** is shown in Figure 20. *Trans*-octahydro-10-methoxybenzo[*f*]quinoline **18** was prepared according to literature methods,[45,46] starting from 8-methoxy-β-tetralone **10**.[47] After the introduction of the nitro function para to the methoxy group, the indole ring was formed by a Leimgruber-Batcho indole synthesis.[48]

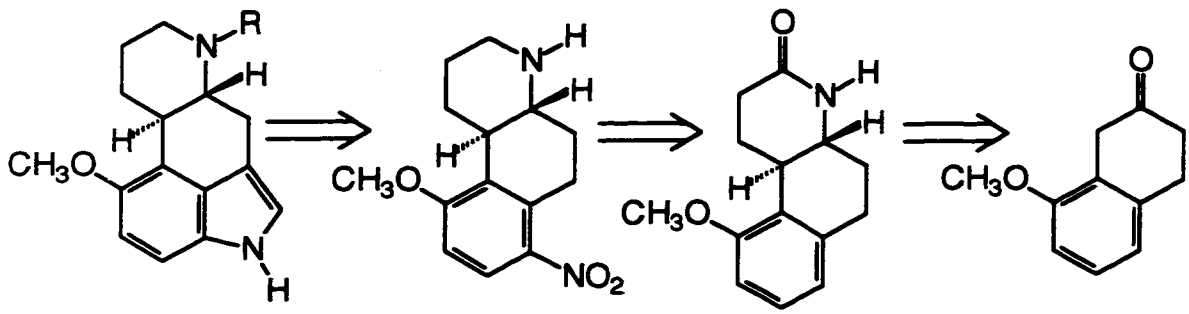


Figure 20. Retrosynthetic scheme for the synthesis of 12-methoxyergolines

The starting material, 8-methoxy-β-tetralone **10**, was prepared from 1,7-dihydroxynaphthalene **8** using a Birch reduction[49] in reasonable yield (Figure 21). During this work, however, **8** became virtually impossible to obtain commercially, so an alternate synthesis was sought. McKervey et al.[50] originally reported that tetralone **10** could be prepared by Rh(II) acetate catalyzed cyclization of the diazo compound (Figure 22). However it was subsequently reported[51] the actual yield of this conversion was much lower (maximally around 20%). In addition to these methods, β-tetralones have been made either by the transposition of the carbonyl group of α-tetralones,[52] or by annelation of phenylacetic acids with ethylene. There have been several reports that β-tetralones including chloro, bromo, methyl, and methoxy substituted analogs were efficiently prepared according to the method of Burckhalter and Campbell[53] by Friedel-Crafts acylation of ethylene followed by intramolecular alkylation. An attempt to prepare **10** from 2-methoxyphenylacetyl chloride by this latter method was not successful.

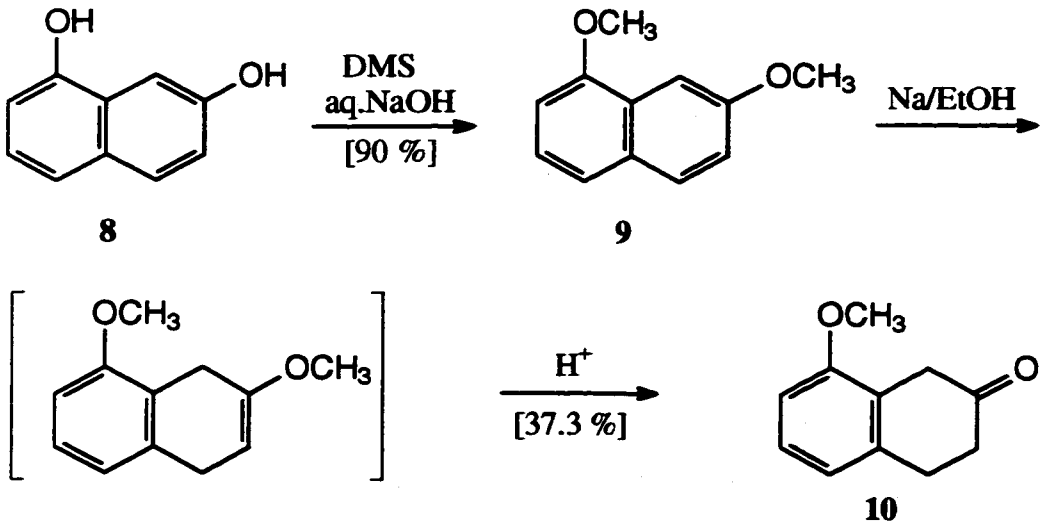


Figure 21. Synthesis of 8-methoxy-β-tetralone **10** *via* a Birch reduction (Method A)[49]

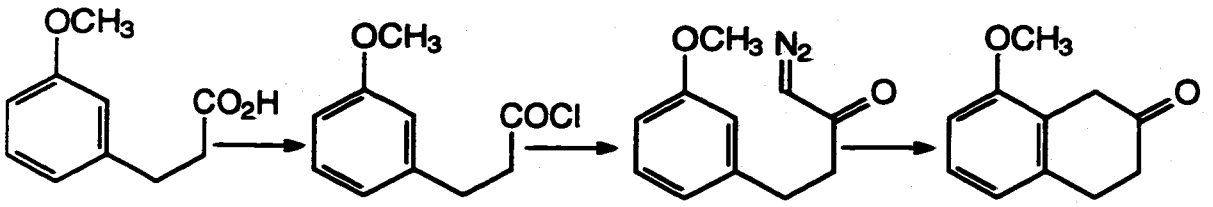


Figure 22. Synthesis of 8-methoxy-ß-tetralone **10** by McKervey's procedure[50]

We next considered the copper(I)-catalyzed exchange reaction of bromide by methoxide, since 8-bromo-β-tetralone **13** can be made in good yield by straightforward methods.[54] However, this nucleophilic substitution reaction appeared to suffer from several problems, such as a lack of selectivity, the need for high temperature, and the requirement for solvents such as HMPT and DMF in the case of unactivated (devoid of electron withdrawing substituents) aryl bromides. However, it has been reported[55] that this exchange can be carried out under mild conditions in concentrated (3 to 5 Molar) methoxide solution, using esters as co-catalysts to prevent the precipitation of copper(I) methoxide. Thus, **10** was prepared by methoxylation of 8-bromo compound **14** in an overall yield of about 50%, starting from commercially available 2-bromophenylacetic acid, **11** (Figure 23).

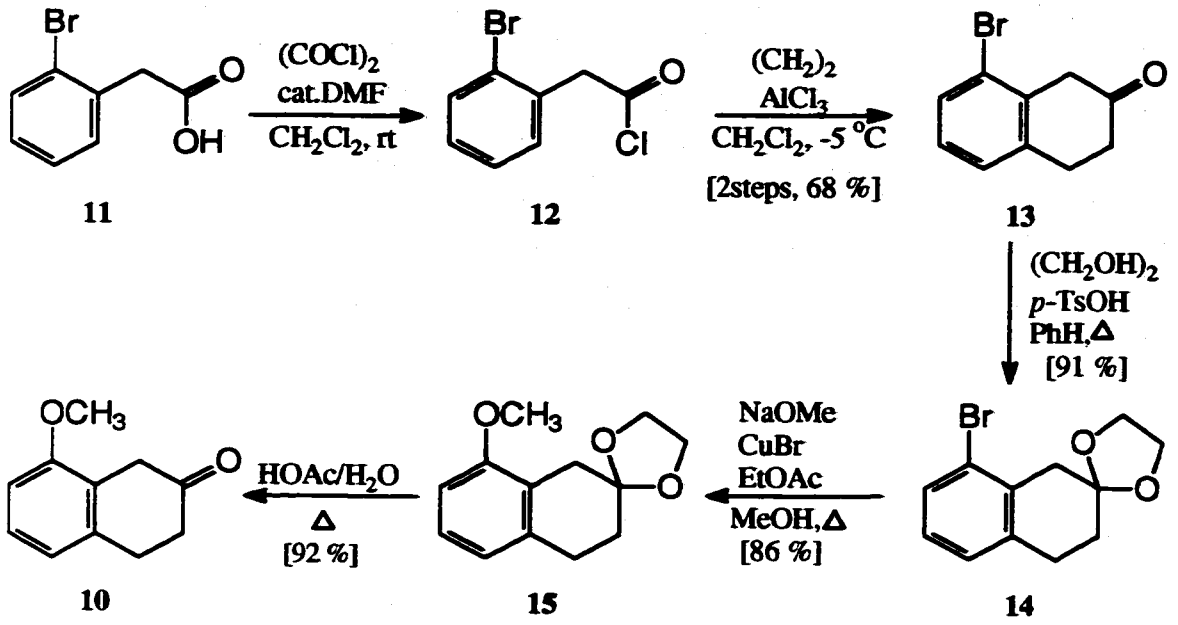


Figure 23. Synthesis of 8-methoxy-ß-tetralone **10** by methoxylation of the 8-bromo compound (Method B)

The enamide, tetrahydrobenzo[*f*]quinolone **17** was synthesized by the Stork-Ninomiya aza-annulation reaction,[56] and reduced to amide **18** with Et_3SiH/TFA to obtain the trans isomer stereoselectively (Figure 24). Octahydrobenzo[*f*]quinolines have been prepared by Hacksell et al.[57] through the reduction of *N*-benzylenamines using $NaBH_3CN$. The 10-methoxy enamine gave an 86:14 cis:trans mixture, while reduction of the 7-, 8-, and 9-methoxy enamines yielded approximately equal amounts of cis and trans isomers. It was postulated that this discrepancy might be due to the steric interaction of the 10-methoxy group with the heterocyclic ring, forcing this ring into a conformation which favors formation of the cis isomer. Later, the same group attempted[45] to improve the stereoselectivity of the synthetic sequence by using Et_3SiH/TFA for the reduction of enamide **17** to amide **18**. It was claimed they were never able to obtain cis:trans ratios

lower than 65:35 under a variety of reaction conditions. The Stork-Ninomiya aza-annulation reaction was reinvestigated by Cannon *et al.*,[46] who showed three tautomeric double bond positional isomers, **17**, **17a**, and **17b**. Cannon *et al.*[46] reported that pure **17** or **17a** gave very high yields (> 90%) of trans-fused isomer, whereas **17b** gave a similarly high yield of the cis product. Pure **17**, prepared from 8-methoxy-β-tetralone in 38% yield after purification using flash chromatography, was reduced to amide **18** which still contained about 30% of the undesired cis isomer. These isomers were difficult to separate and were carried to the next step.

Most aromatic nitrations, as classically performed with mixtures of nitric and sulfuric acids, give predominantly ortho and para products. Quite often their distribution is close to the statistical 2:1 ratio.[58] It was desirable to improve the regioselectivity, pushing it toward a higher proportion of the para product to obtain **19** in high yield. The reagent "claycop", an acidic montmorillonite clay impregnated with anhydrous cupric nitrate, has shown to provide high nitration yields and selectivities.[59] The nitration of anisol by claycop in CCl_4 and acetic anhydride was reported to yield 52% of 4-nitroanisole and 44% of 2-nitroanisole.[60] A 4:1 ratio between para (7-nitro-) and ortho (9-nitro-) isomers was obtained when **18** was nitrated using the procedure, but in total nitration yield of only 29%.

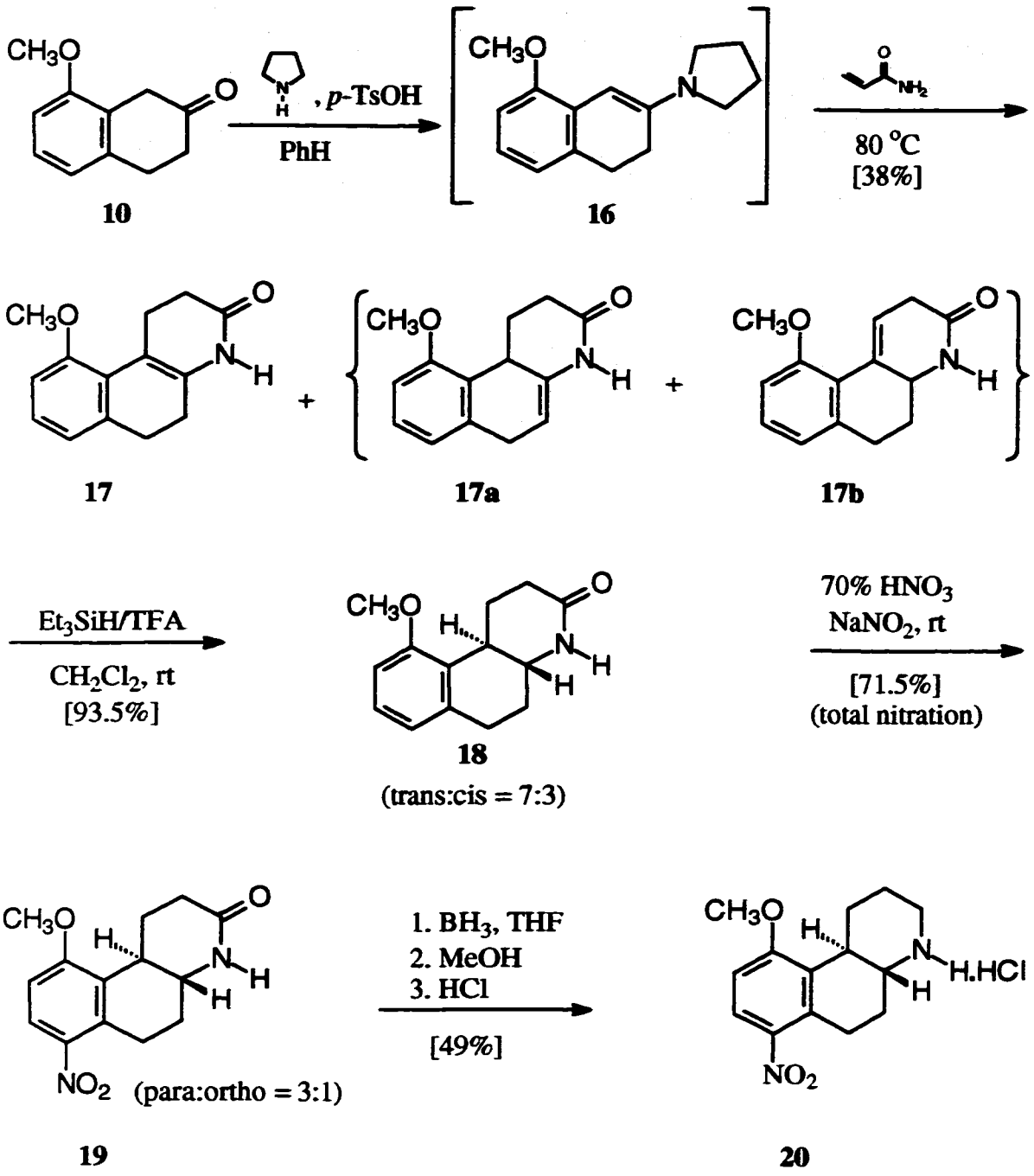


Figure 24. Synthesis of octahydrobenzo[*f*]quinoline

It has been proposed that the nitrosoanisoles might be intermediates because of para selectivity in the nitrite-catalyzed reaction in nitric acid.[61] The nitration of **18** in 70% nitric acid with sodium nitrite gave a 71.5% yield of total nitration, and a 3:1 ratio of para:ortho isomers. Because a trans:cis mixture of **18** was used, the crude product was comprised of four isomers; *cis*-7-nitro-, *trans*-7-nitro-, *cis*-9-nitro-, and *trans*-9-nitro in that elution sequence upon column chromatography. Because the *cis*-7-nitro-isomer, which was present in a relatively small amount compared to the *trans*-7-nitro-isomer **19**, seemed to be more crystallizable than the *trans*-7-nitro-isomer, it was difficult to purify **19** by crystallization. Flash chromatography separated all isomers except the *cis*-9-nitro-isomer, which was present only in a very small amount. The *trans*-7-nitro-isomer **19** was finally obtained in 37.5% from the mixture of isomers **18**. The amide **19** was reduced to the amine **20** in 49 % yield with BH_3.

Although the Leimgruber-Batcho indole synthesis[48] was described in 1971, only nitrotoluenes but not other alkylnitrobenzenes are well known as C-H-acidic components. The condensation reaction of 5-nitrotetralin (Figure 25) with Bredereck's reagent, *tert*-butoxy-bis(dimethylamino)methane followed by reduction, was reported to form 1,3,4,5-tetrahydrobenz[c,d]indole in 40% yield over both steps.[62] Bredereck's reagent was proposed to be superior to *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) due to the greater alkoxide concentration and the greater basicity of the tertiary butoxide ion.

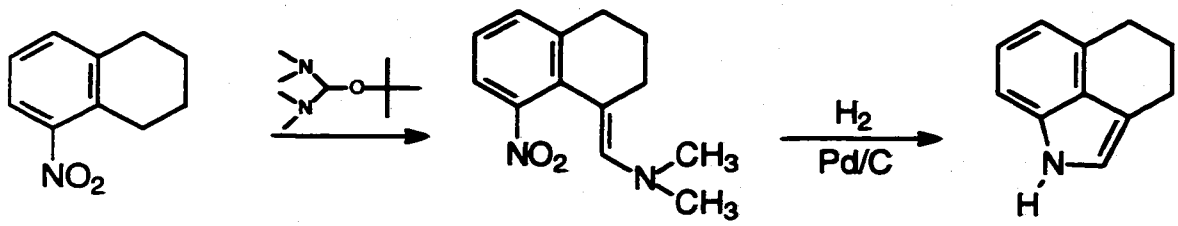


Figure 25. Leimgruber-Batcho Indole Synthesis of nitrotetralin[62]

The reaction of **20** with DMFDMA did not work well, therefore tripiperidinomethane (TPM) **21** was applied as a replacement for DMFDMA. The TPM condensation followed by reductive cyclization with nickel boride/hydrazine hydrate, was developed in our laboratory to provide indoles in good yields.[63] TPM was easily prepared by the method of Swaringen *et al.*[64] Compound **20** was treated with TPM, and the resulting nitropiperidinostyrene **22** was reduced with nickel boride/hydrazine hydrate to form 12-methoxyergoline **1** in 28% yield (Figure 26). *N*-Methyl-**2**, and *N*-propyl-**3** derivatives were prepared by conventional methods.

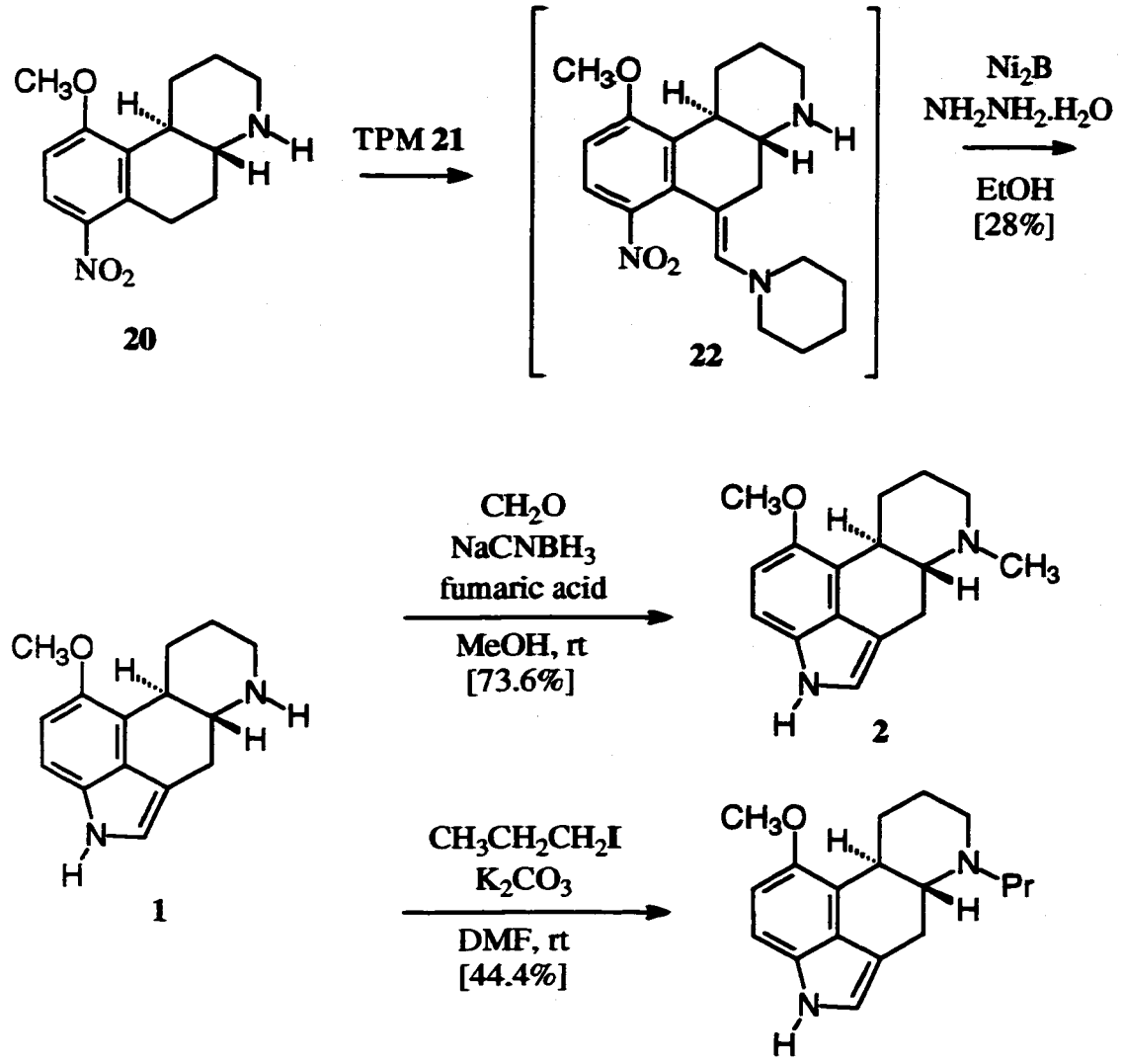


Figure 26. Synthesis of 12-methoxyergolines *via* a Leimgruber-Batcho indole synthesis

13-Hydroxybenzergolines

Approaches to formation of ring C

The synthesis of benzergolines was reported[38,65] by using the Ninomiya enamide photocyclization reaction (Figure 27),[66] which was applied to the synthesis of dihydrexidine[67] in our laboratory. *N*-benzoyl-4-keto-hexahydrobenz[*c,d*]indole prepared from its 5-keto derivative,[6] was used as an intermediate. To prepare 2-hydroxybenzergolines **4-6**, we initially attempted to synthesize the 7-methoxy-4-keto tricyclic compound **38** (Figure 32), following a modification of the route reported for Kornfeld's ketone (Figure 3).

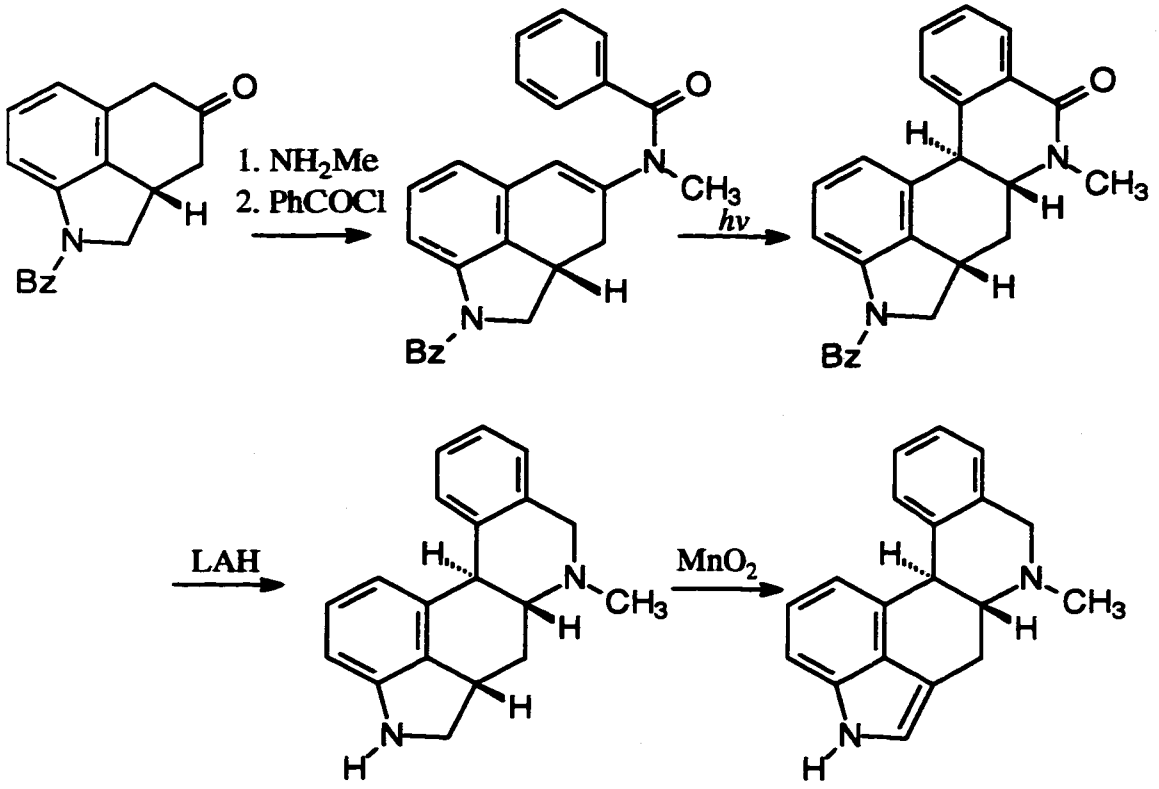


Figure 27. Synthesis of benzergolines[65]

6-Methoxyindole **28** was obtained using the Hemetsberger reaction[68] (Figure 28). *Para*-methoxybenzaldehyde was treated with methyl azidoacetate **23**, obtained according to a literature procedure,[69] to yield the azidocinnamate **25**, which was thermally cyclized to the indolecarboxylate **26**. The ester was hydrolyzed to the acid **27**, and copper-catalyzed decarboxylation gave the indole **28**. Diverging from the literature methodology of the decarboxylation, *N*-methylpyrrolidinone was used as the solvent, which is easily removed in the workup, rather than quinoline. In spite of the slightly lower yield and longer reaction time, it was still considered advantageous to avoid the use of quinoline.

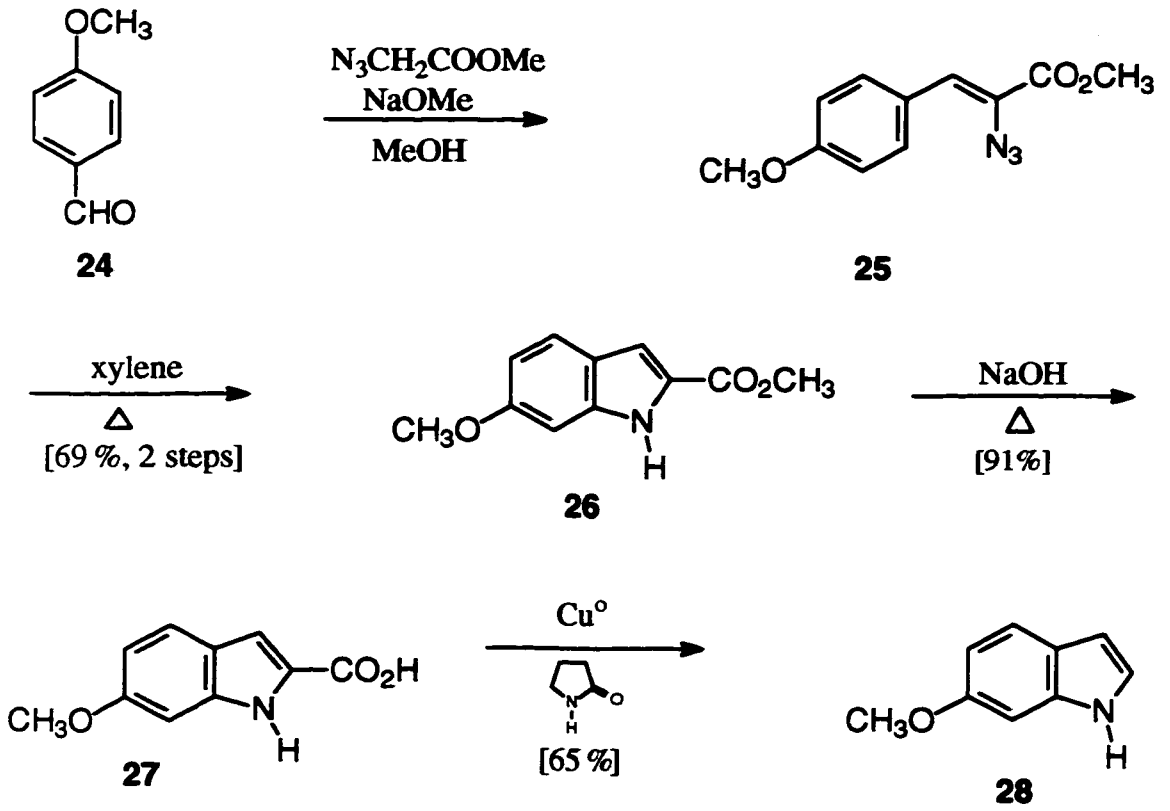


Figure 28. Synthesis of 6-methoxyindole

Since the original synthetic work of Kornfeld *et al.* [6] on lysergic acid, the 5-keto-tricyclic compound (Kornfeld's ketone, Figure 3) and its 4-keto derivatives still remain, perhaps, as the most versatile intermediates for the synthesis of ergolines. To obviate the lengthy intermediacy of 5-keto-isomer **45** (Figure 34), we attempted to prepare 4-keto-isomer **38** *via* intramolecular homoacylation of 6-methoxyindole-3-acetic acid derivatives.

6-Methoxyindole-3-acetic acid methyl ester **32** was prepared using a literature procedure[70] from 6-methoxyindole through gramine **29**, gramine methiodide, nitrile **30**, and acid **31** (Figure 29). Although each step proceeded smoothly and in a good yield, this was still considered to be a long synthetic sequence to prepare a starting material. Attempts to obtain **32** directly by Fischer-indole synthesis[71] (Figure 30) from 3-methoxyphenylhydrazine hydrochloride **34** were not successful. The use of zinc salts of indoles is the preferred method for producing indole 3-alkylation or acylation without complication by reaction at the 1-position.[72] The introduction of an acetic acid ester group into the indole 3-position by reacting the zinc salt of indole has been reported.[73] The treatment of the zinc salt of **28** with methyl 2-bromoacetate gave **32** in 40.3% yield. Even though the yield was not high, this route had the advantage of being a one step reaction compared to the above long synthesis. In addition, 49% of the starting material was recovered. The indole **32** was reduced to the indoline with $NaCNBH_3$ in acetic acid, and then immediately protected with *p*-TsCl to yield **33**.

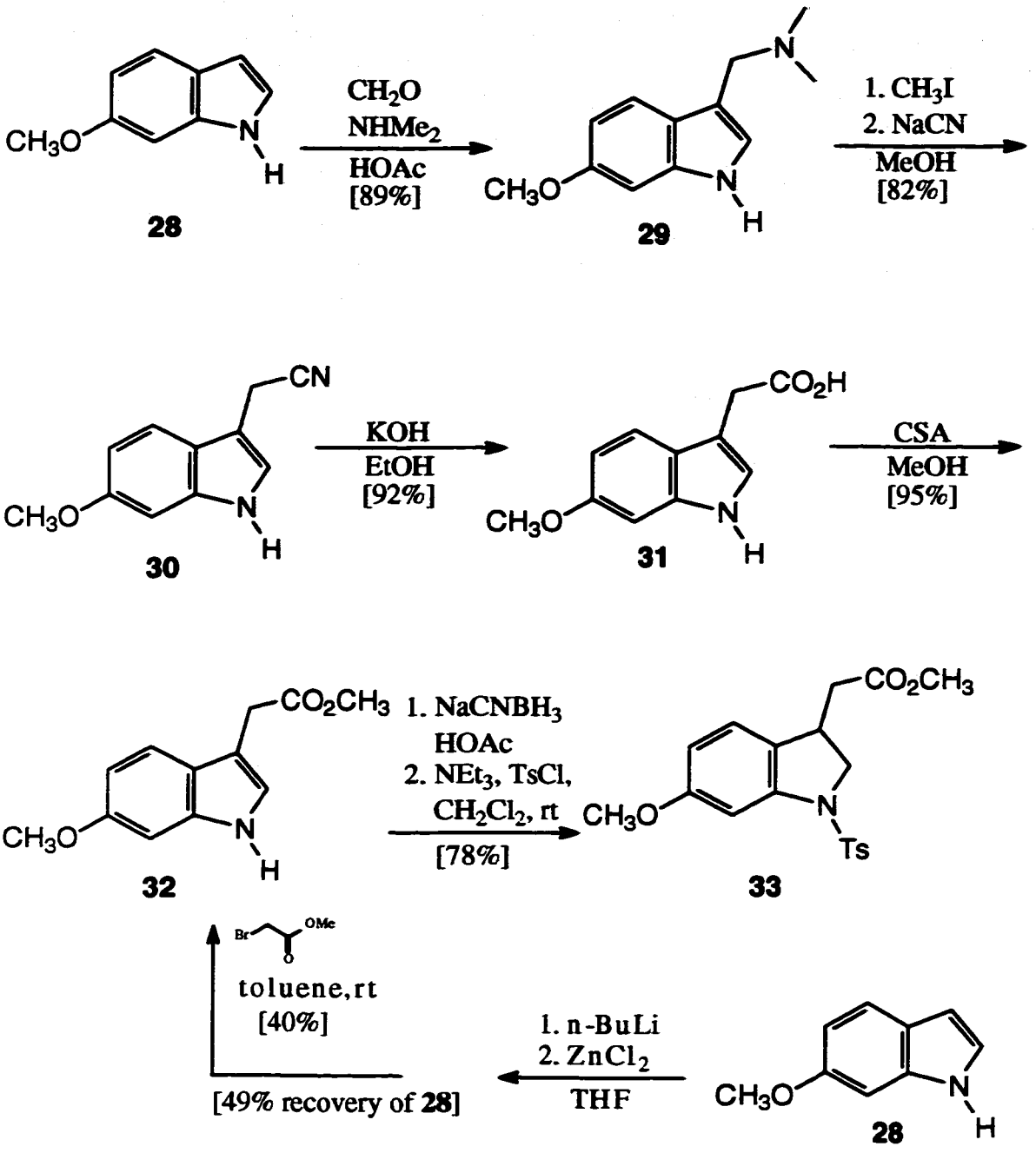


Figure 29. Synthesis of 6-methoxyindole-3-acetic acid derivatives

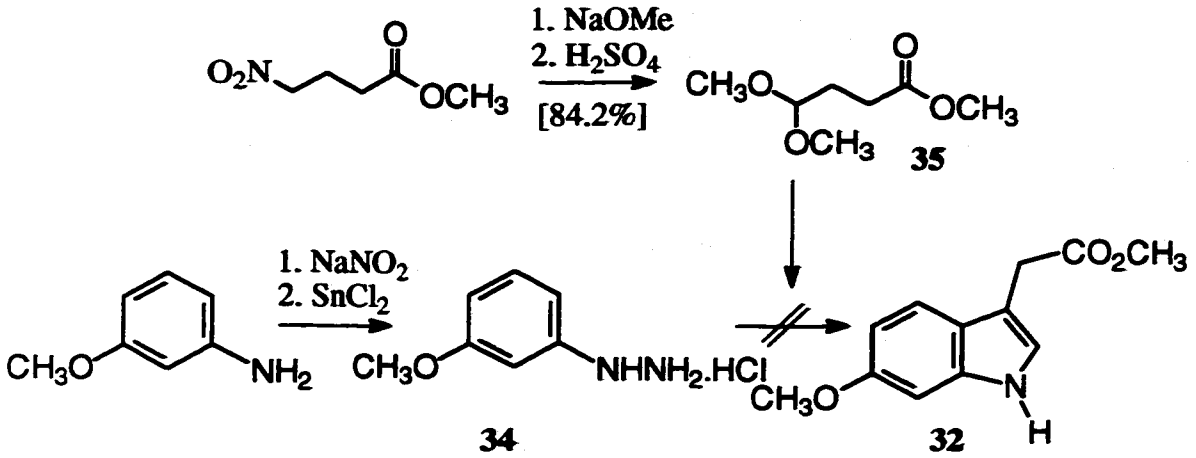


Figure 30. Attempted Synthesis of 6-methoxyindole-3-acetic acid *via* Fischer-Indole Synthesis

Intramolecular C-H bond insertion by diazoketones has become an excellent methodology to construct cyclic ketones.[74] Metal-catalyzed intramolecular cyclization of 2-diazo-4-(4-indolyl)-3-oxobutanoic acid esters has been studied,[75] which led to indoles with a C-ring *via* C-H bond insertion (Figure 31). The Rh-catalyzed reaction of the diazoketone yielded the tricyclic compound which was cyclized at the 5-position of indole, not at the reactive 3-position. It was explained that Rh-catalyzed cyclization would prefer substantially for five-membered ring formation, having a six-membered ring transition state. On the other hand, six-membered ring formation would require a seven-membered transition state, which was probably less stable than the six-membered one, and that might be a reason for the regioselectivity. On the other hand, Pd-catalyzed reaction gave a completely different result. The Pd-catalyzed cyclization at the 3-position was significantly affected by the *N*-substituent of indole; a 71% yield without a protecting

group *versus* no product with *N*-tosyl protection. It was suggested that carbocationic species would participate in the Pd-catalyzed reaction. The attempted Pd-catalyzed reaction of the diazoketone **37** failed to provide any cyclized product **38**, probably due to the poor electronic effect of the 4-position (Figure 32). The Rh-catalyzed reaction of **37** yielded several products, which included a small amount of cyclized product **38**.

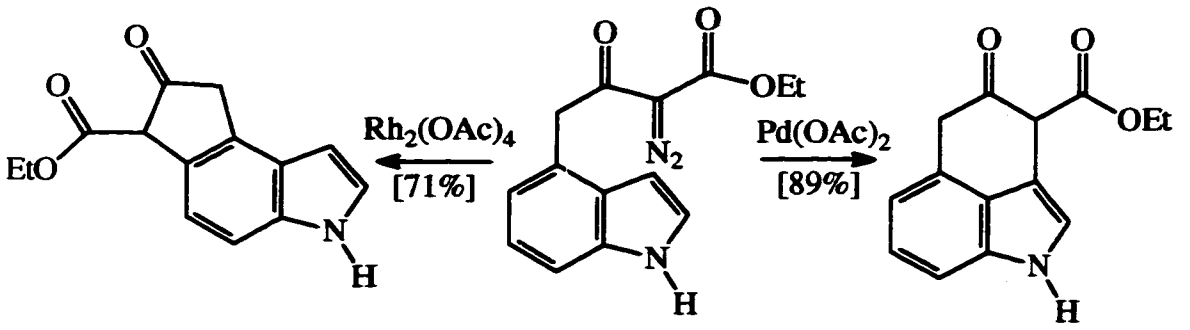


Figure 31. Metal-catalyzed cyclization of 2-diazo-4-(4-indolyl)-3-oxobutanoic acid[75]

The preparation of the 8-methoxy derivative of the tricyclic 4-ketobenz[*c,d*]indoline *via* a Pummerer intermediate has been reported.[76] In that report, 7-methoxy-1-(benzenesulfonyl)-indoline-3-acetic acid ethyl ester was converted to the β-keto sulfoxide using the lithium salt of DMSO, which was subsequently cyclized to the 4-position of the indoline using trifluoroacetic anhydride in the presence of Lewis acid, followed by desulfurization with Raney nickel to provide the target ketone in 70% overall yield. Compound **33** was converted to the β-keto sulfoxide **39** in 74% yield. The attempted intramolecular cyclization reaction of **39** under Pummerer reaction conditions, however, formed an intractable mixture of products (Figure 32). Recently, it has been

reported[77] by the same research group which prepared the 8-methoxy-4-keto-tricyclic compound that the intrahomoacylation of unsubstituted indoline to the tricyclic ketone *via* Pummerer intermediates under various reaction conditions gave at least five major products.

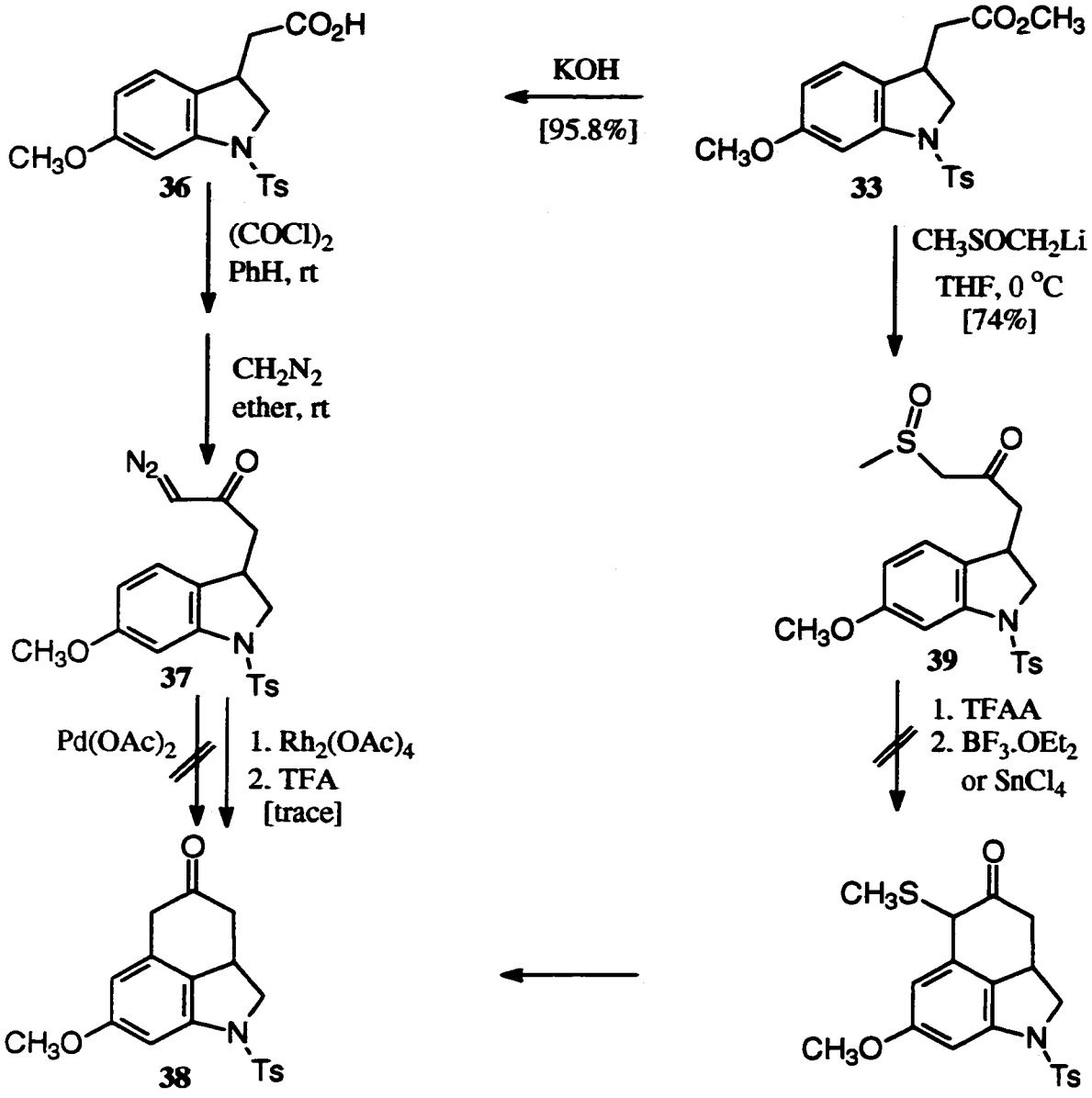


Figure 32. Proposed synthesis of the 6-Methoxy-*N*-tosyl tricyclic ketone *via* homoacylation

The Kornfeld group[6] prepared the tricyclic ketone (Figure 3) from *N*-benzoylindoline-3-propionic acid through the corresponding acid chloride and a Friedel-Crafts acylation. Due to the failure of the attempted homoacylation reactions, the preparation of the 5-keto-tricyclic compound **45** was considered. The procedure of carbonyl transposition[78] which converts the 5-keto-isomer **45** to the 4-keto-isomer **38**, is well established in our laboratory and comprises four high yielding steps; the reduction of ketone to the alcohol, dehydration, epoxidation, and ZnI_2 catalyzed epoxide ring opening, resulting in the transposed ketone.

It has been known[79] that Meldrum's acid **40** and formaldehyde condense very efficiently with indoles when the molar ratio of these three reactants is 1:1:1. Using that procedure, lactone **41** was obtained from 6-methoxyindole in 81.6% yield. Subsequently, the decarboxylative ethanolysis of **41** gave 6-methoxyindole-3-propionic acid **42** (Figure 33). Since the presence of copper salts remaining in the product mixture, even after filtration, gives rise to a severe air sensitivity, the copper salts were immediately washed out with ammonium chloride solution. The indole **42** was reduced to the indoline, protected to yield *N*-tosyl-indoline-3-propionate **43**, and hydrolyzed to acid **44**.

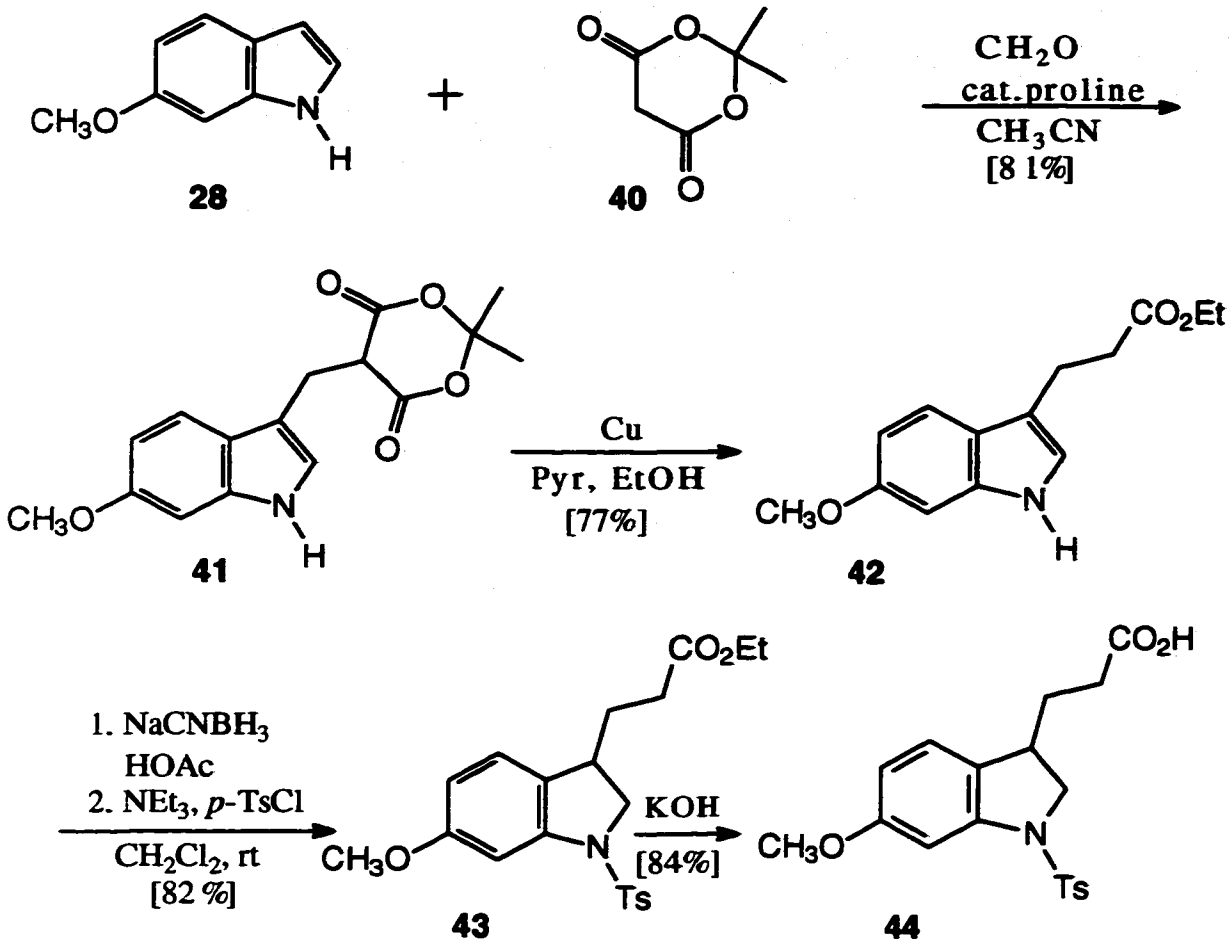


Figure 33. Synthesis of 6-methoxyindole-3-propionic acid derivatives

Attempts to effect cyclization of acid **44** to **45** with PPA or HF in pyridine were unsuccessful. With trifluoroacetic anhydride in CH_2Cl_2 only a very small conversion was obtained. The acid **44** was converted to the acid chloride **46**, which was treated with both $AlCl_3$ and $SnCl_4$. No reaction conditions could be identified, however, where Friedel-Crafts acylation reactions provided any significant yield of **45**. The reduction of the ester **43** with DIBAL in CH_2Cl_2 yielded the aldehyde **47**, which is also a reactive species for Friedel-Crafts reaction. Attempted reactions to form ring C with aldehyde **47** were

likewise unsuccessful. Kornfeld synthesized the unsubstituted tricyclic ketone[6] from the acid chloride by reflux with $AlCl_3$ in carbon disulfide. Due to the lability of the methoxy substituent to $AlCl_3$ dealkylation, all Friedel-Crafts reactions of 6-methoxy indole derivatives **44**, **46**, **47** were attempted at lower temperature than rt, and none were successful (Figure 34).

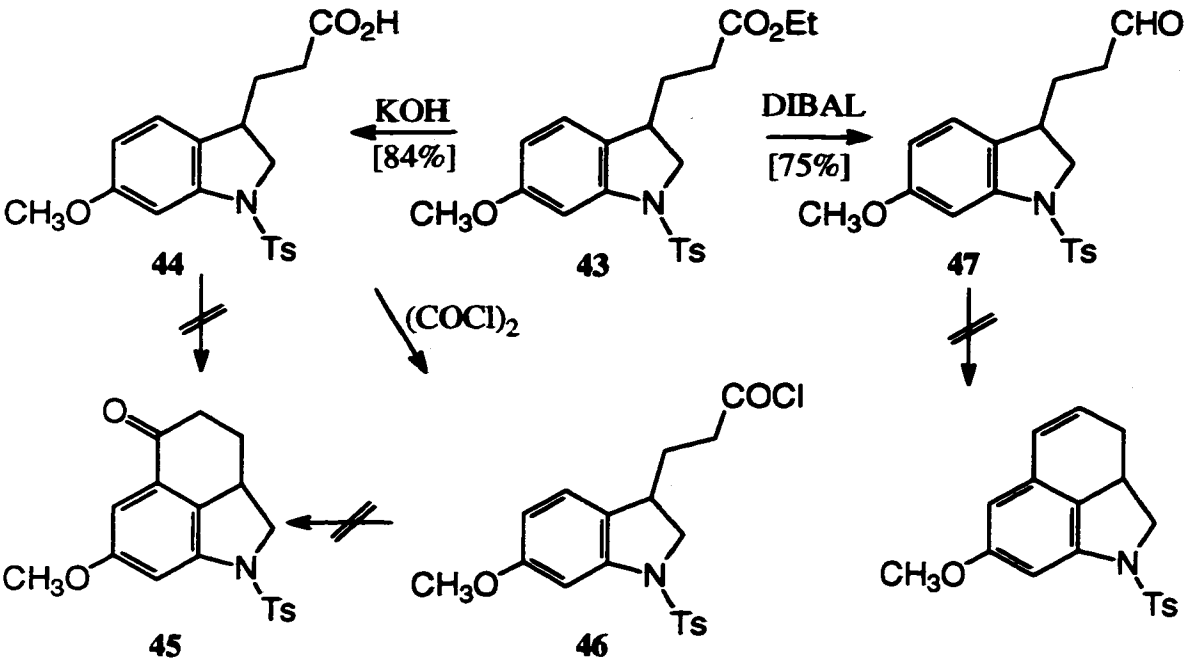


Figure 34. Attempted Friedel-Crafts reactions of indole-3-propionic acid and proposed derivatives

To prepare 3,4-dihydrobenz[*c*,*d*]indol-5(1*H*)-one (Uhle's ketone, Figure 4), direct cyclization at the 4-position of 3-(indol-3-yl)propionic acid, not from the indoline, has been reported.[80] Usually, cyclization does not take place at the desired 4-position, because of the much greater nucleophilic reactivity of the 2-position over the 4-position.

Teranishi *et al.*[80] found that the characteristic chemical shift of aromatic proton H-7 of 1-trimethylacetylindole-3-propionic acid, appeared at lower field (8.50 ppm) in the ^{1}H NMR spectrum, because of the effect of the carbonyl group being close to proton H-7. Moreover, *t*-butyl protons of the trimethylacetyl group and proton H-2 of the compound are close enough to give a NOE (10%). It has been postulated that the 2-position of indole should be inactivated by addition of a stronger electron acceptor. By the combination of an *N*-pivaloyl protecting group and addition of chloroacetyl chloride as an electron acceptor, it was reported that Friedel-Crafts cyclization with aluminum chloride regioselectively gave Uhle's ketone derivative in good yield.[80] The same procedure was applied to the *N*-trimethylacetyl-6-methoxyindole-3-propionic acid but starting material was mostly recovered (Figure 35).

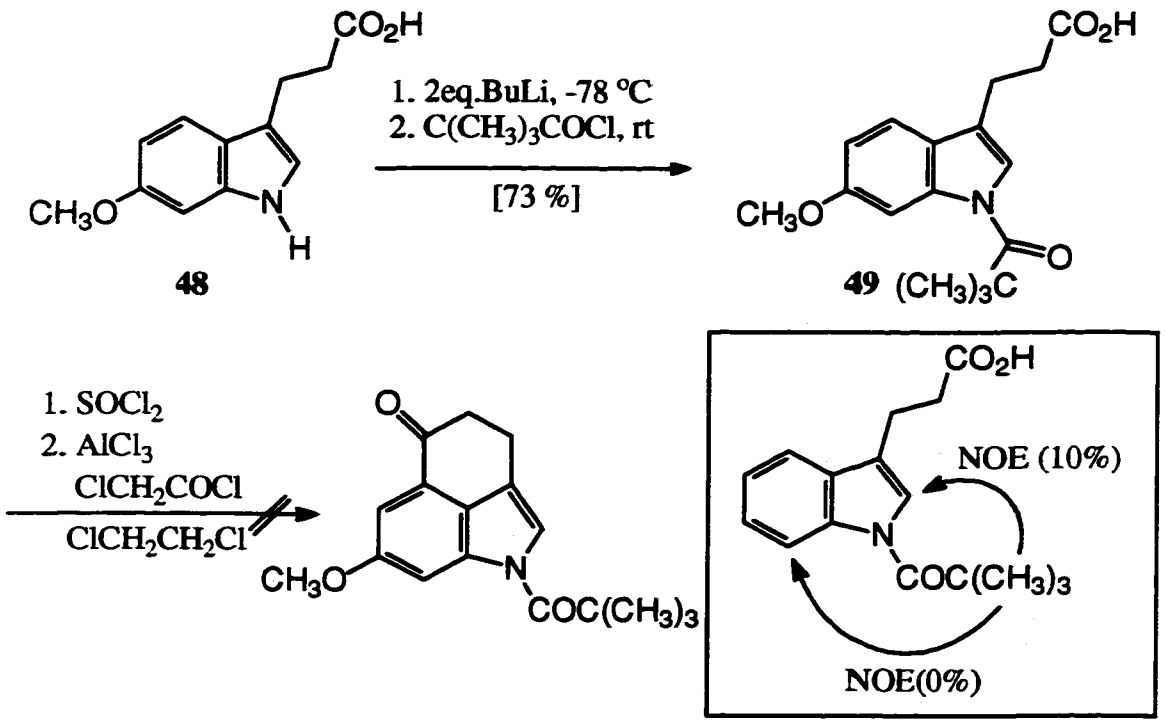


Figure 35. Attempted Friedel-Crafts Reaction *via* *N*-pivaloyl protection

It is well known that a methoxy group on the benzenoid moiety *ortho* or *para* to the reaction center activates electrophilic substituion reactions including Friedel-Crafts reactions. The effect of a methoxy substituent at the *meta* position is not well studied. Nevertheless, the failure of virtually every attempt to effect electrophilic attack at the 4-position of 6-methoxyindole and its derivatives would seem to be explainable only by a powerful deactivating effect at the position *meta* to the methoxy group. Besides the low reactivity of the 4-position of 6-methoxyindole, a high degree of strain in the molecule on fusion of the 6-membered ring C might also contribute to the failure of the above attempts.

Approaches *via* an indole tricarbonylchromium(0) complex

Approaches to formation of ring C by intramolecular cycloaddition at the 4-position of indoles were not successful. In fact, electrophilic reactions occur with good selectivity at C-3, metallation can activate C-2, and less general methods[81] have been employed to add carbon units at C-4 due to the low nucleophilicity of the 4-position compared to the other positions.

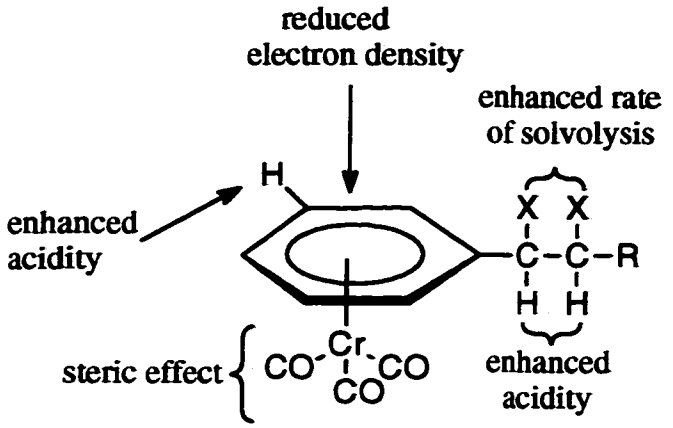


Figure 36. Effects on arene reactivity of metal coordination[82]

The addition of carbon nucleophiles to η^6-arenetricarbonylchromium(0) compounds including indoles, and subsequent oxidation has become a useful method for introducing substituents in positions not accessible by electrophilic substitution.[82] General changes in reactivity (Figure 36) of arenetricarbonylchromium complexes are as follows: 1) Steric effects of the metal-ligand system, 2) stabilization of side chain cationic sites (benzyl and phenethyl cation), 3) stabilization of side chain anion sites (benzyl anion), 4) enhanced

acidity of the arene ring hydrogen, and 5) addition of nucleophiles to the arene π-system leading to nucleophilic aromatic substitution. A most dramatic effect is the powerful withdrawal of electron density from the aromatic ring, much like the effect of a nitro substituent in the sigma bond framework. The addition of a nucleophile to *N*-protected indole-$Cr(CO)_3$ complex has been shown[83] to allow regioselective nucleophilic substitution at C-4 or C-7 on the indole ring, depending on the substituents at C-3 and N-1, as well as the nature of the nucleophile. Bulky protecting groups, *N*-*t*-butyldiphenysilyl or *N*-triisopropylsilyl, drive substitution at the 4-position rather than the 7-position.[84] In addition, meta substitution is always preferred[85] while strong resonance donors such as alkoxy, or amino, may provide more regioselectivity for substitution at C-4 of 6-methoxyindole.

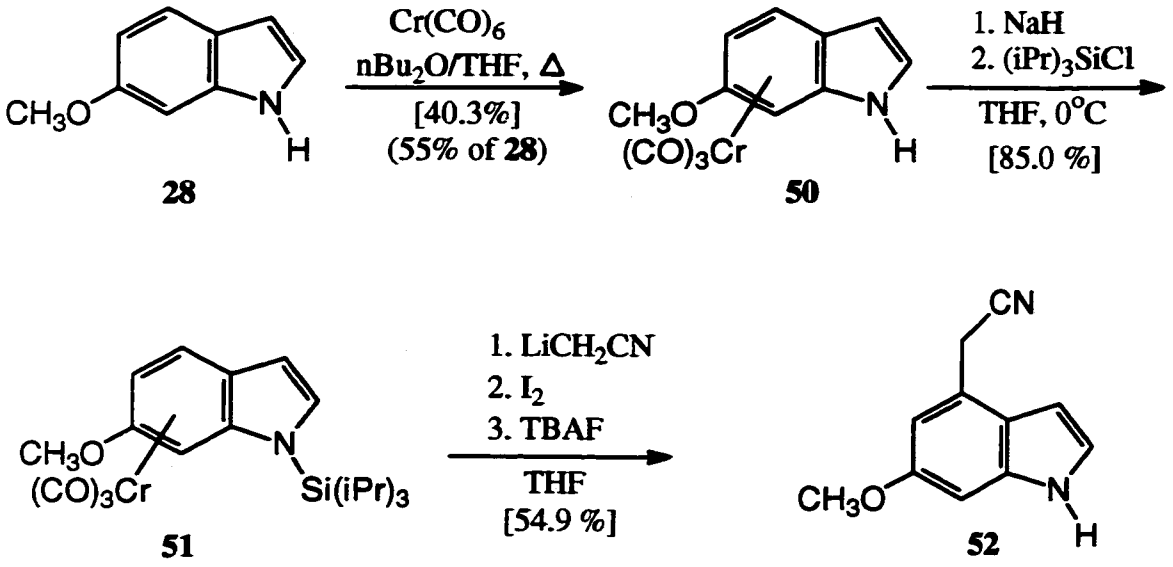
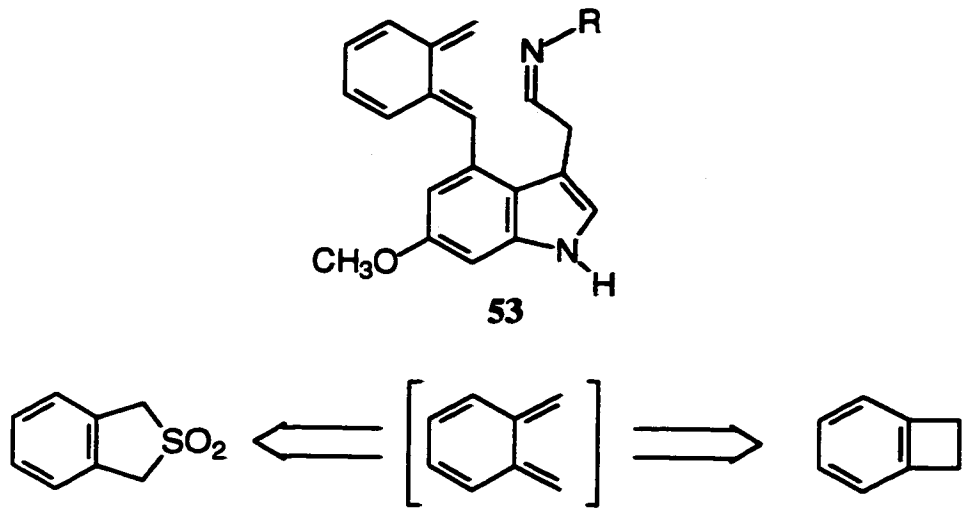


Figure 37. Nucleophilic substitution of indole chromium complex

6-Methoxyindole **28** was transformed into the corresponding tricarbonylchromium complex **50** in 40.3% yield with 55% recovery of **28** (Figure 37). The incomplete conversion is probably due to the volatility of $Cr(CO)_6$, which has been improved[86] by the use of a Strohmeier apparatus.[87] Various solvents have been studied[88] to speed up the reaction and for easy workup. The most commonly used solvent, a mixture of dibutyl ether and THF (10:1) to catalyze the reaction and to wash back most of the $Cr(CO)_6$ that sublimes into the condenser, was used. The chemical shifts in the NMR spectra of the aromatic hydrogens of **50** were shifted upfield compared to **28**. Complex **50** was silylated with triisopropylchlorosilane to produce the orange, crystalline **51** in 85% yield. The addition of **51** to a solution of the lithiated acetonitrile, followed by oxidative quenching with iodine and desilylation furnished 4-substituted indole **52** in 54.9% yield. Other regioisomers of **52** were not found. With a bulky *N*-protecting group and *meta*-methoxy substituent, the 4-position appears to be favored.

With the above result, it was planned to introduce nucleophiles into the 4-position of indole, which are suitable for heteroatom Diels-Alder cyclization with readily available substituents at the 3-position, resulting in the rapid construction of the benzergoline ring system. Oppolzer *et al.*[13] have devised a clever total synthesis of lysergic acid which has as its key step an itramolecular imino Diels-Alder reaction (Figure 8). A retro-Diels-Alder reaction occurred, liberating cyclopentadiene that was cyclized to give a tetracyclic ergoline as a 3:2 mixture of diasereomers. Normally oximes are not reactive dienophiles, but clearly the intramolecularity of the conversion is crucial to the success of this transformation. The intramolecular cycloaddition reactions between *o*-quinodimethanes

generated from benzocyclobutenes or sulfones and with dienophiles has been reviewed.[88] Compound **53**, which has an *o*-quinodimethane moiety at the 4-position of indole (Figure 38), would be a valuable intermediate for the synthesis of benzergolines **4-6**.



53

Figure 38. Proposed intermediate for the synthesis of benzergolines by a Diels-Alder reaction

The condensation reaction of 1-cyanobenzocyclobutene with 3-bromopropan-1-ol in the presence of LDA, and then reductive decyanation with sodium in liquid ammonia, has been reported.[89] Therefore, the introduction of a benzocyclobutene moiety into the 4-position of indole using commercially available 1-cyanobenzocyclobutene was attempted (Figure 39). The reaction of **51** and lithiated 1-cyanobenzocyclobutene **54** gave a mixture of 6-methoxyindole **28** and 6-methoxy-*N*-triisopropylsilylindole **56** instead of **55**, however, after oxidative quenching but without treatment with fluoride. It has been reported[82] that

unreactive anions failed to give significant conversion; useful anions were formed from carbon acids with $pK_a > 20$. The benzylic cyano anion **54** doesn't appear to be nucleophilic enough for the reaction.

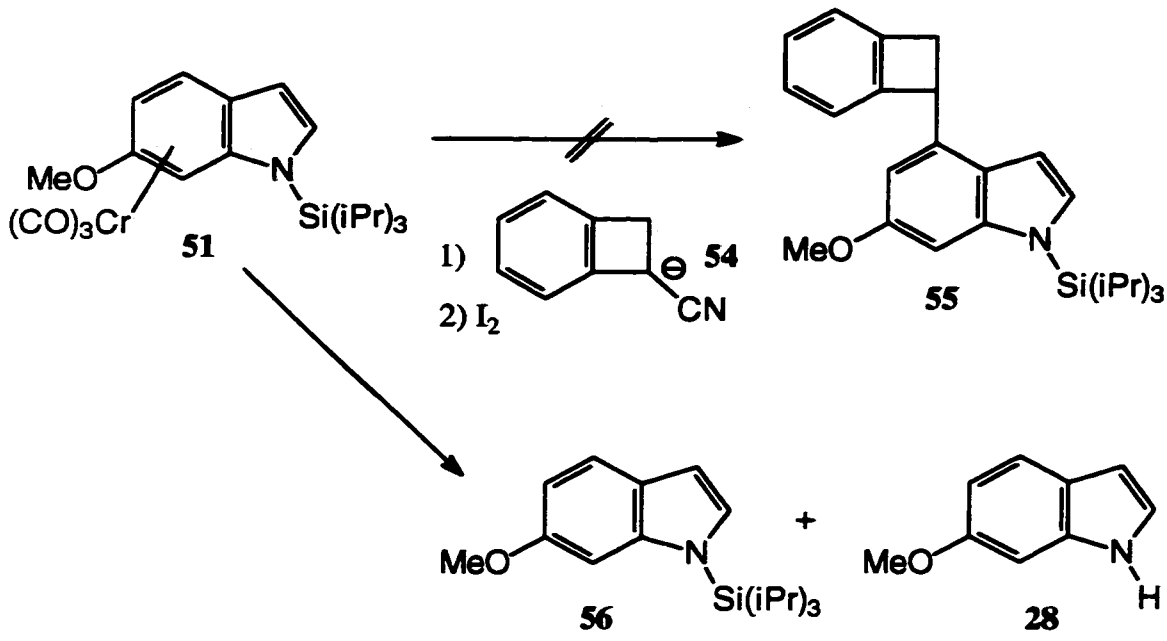


Figure 39. Attempted synthesis of 4-substituted indole with a benzocyclobutene moiety

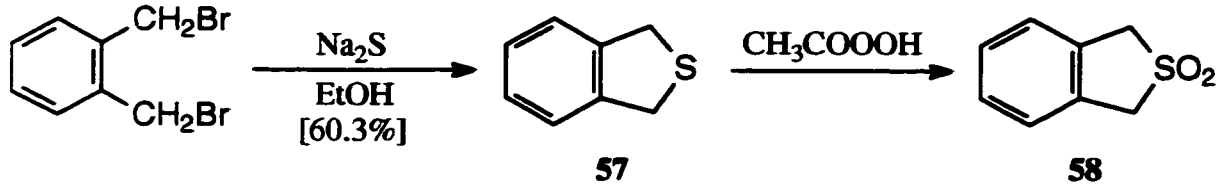


Figure 40. Preparation of 1,3-dihydroisothianaphthene

The synthesis of polycycles based on the intramolecular capture of *o*-quinodimethanes generated by cheleotropic elimination[90] of SO_2 from sulfones has been described.[91] The sulfone **58** may be even more acidic than **54**, therefore, the less acidic **57** was prepared following a literature procedure[92] (Figure 40), and was employed as a carbon nucleophile. The coupled compound **59** was to be converted to sulfone with peracetic acid. But as soon as **57** was treated with base, the reaction mixture turned black. No thianaphthene **57** could be recovered, suggesting decomposition by a ring opening mechanism as shown in Figure 41.

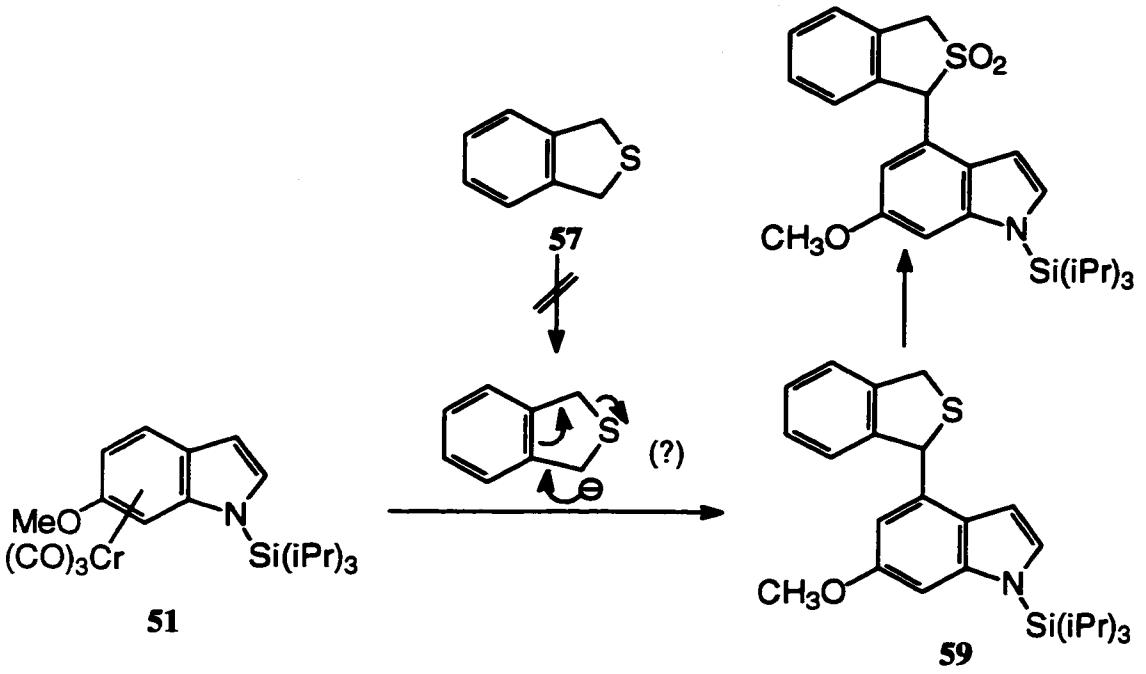


Figure 41. Proposed synthesis of 4-substituted indole with a sulfone moiety

The electron withdrawing effect of an appended tricarbonylchromium group renders the ring susceptible to deprotonation as well as nucleophilic addition.[93] The

combination of chromium-induced lithiation/electrophilic quench, lithiation/trans-metallation/electrophilic quench or lithiation/transmetallation/palladium catalyzed cross coupling has been studied to give access to a wide range of 4-substituted indoles.[94] Therefore, metallation was considered to introduce a substituent at the 4-position. The lithiation of *N*-triisopropylsilylindole-chromium complexes has been reported[95] to give 4-substituted indole with small amounts of 5- and 6-substituted species. Lithiation of compound **51** and quenching with methyl 2-bromoacetate (Figure 42) yielded the desilylated 5-substituted compound **60** rather than the desired 4-substituted compound, based on analysis of the ^{1}H NMR spectrum.

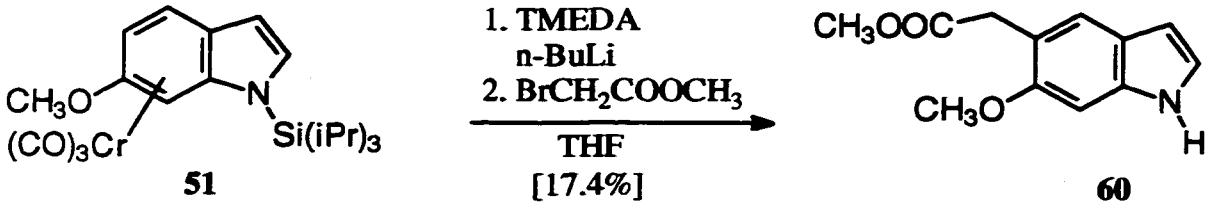


Figure 42. Metallation of 6-methoxyindole-chromium complex.

6-Methoxyindole-4-acetonitrile **52** can be used as an intermediate for the synthesis of benzergolines, but complicated problems such as stability, protection, etc., were anticipated. And therefore, no further attempts employing chromium complexes were made. Still, the chemistry of arene-chromium complexes is an attractive strategy for the regio- and stereoselective total syntheses of polycyclic rings, including ergoline alkaloids.

Approaches *via* a 4-substituted indole

With the complicated problems encountered to this point for the total synthesis of the target molecules **1**, **2** and **3**, a new retrosynthetic analysis was performed. The benzergoline compounds are simply constituted with two synthons; indole and isoquinoline (Figure 43). Coincidentally, isoquinoline-*O*-triflate **76** was developed in our laboratory for another project. It was thus envisioned that **76** could be used with boronic acid **68** to assemble the elements of the benzergoline structure by Suzuki cross-coupling.

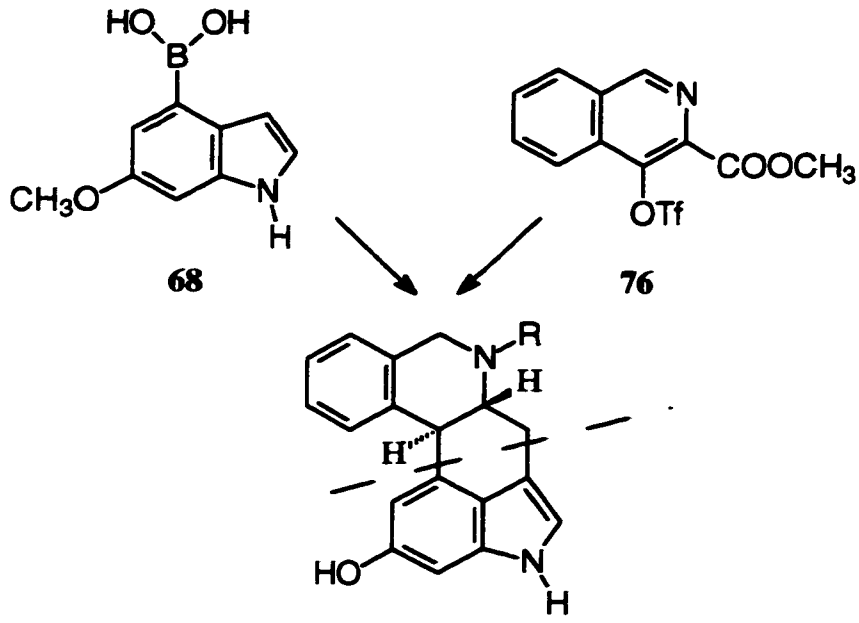


Figure 43. Disconnection of benzergoline into two synthons; indole and isoquinoline

The benzaldehyde **62** was required to prepare 4-bromo-6-methoxyindole *via* a Hemetsberger reaction.[68] There are two published methods for the synthesis of **62**. One

method used ortho directed lithiation of protected *p*-methoxybenzaldehyde with dimethylacetal using *t*-BuLi, followed by quenching with Br_2, without reporting a yield.[96] That lithiation reaction did not appear practical to prepare a large quantity of starting material. Therefore, **62** was prepared by the other literature procedure.[97] Formylation of 3-bromoanisole **61** gave a 2:1 ratio of two isomers, **62** and **63** based on analysis using ^{1}H NMR spectroscopy. The crude mixture was treated with $AlCl_3$, leading to the selective *O*-demethylation of compound **63** by coordination of $AlCl_3$ with the formyl group located at the ortho position. Phenol **64** was easily separated by extraction with base, and the desired benzaldehyde **62** was obtained in overall 48% yield from **61** (Figure 44).

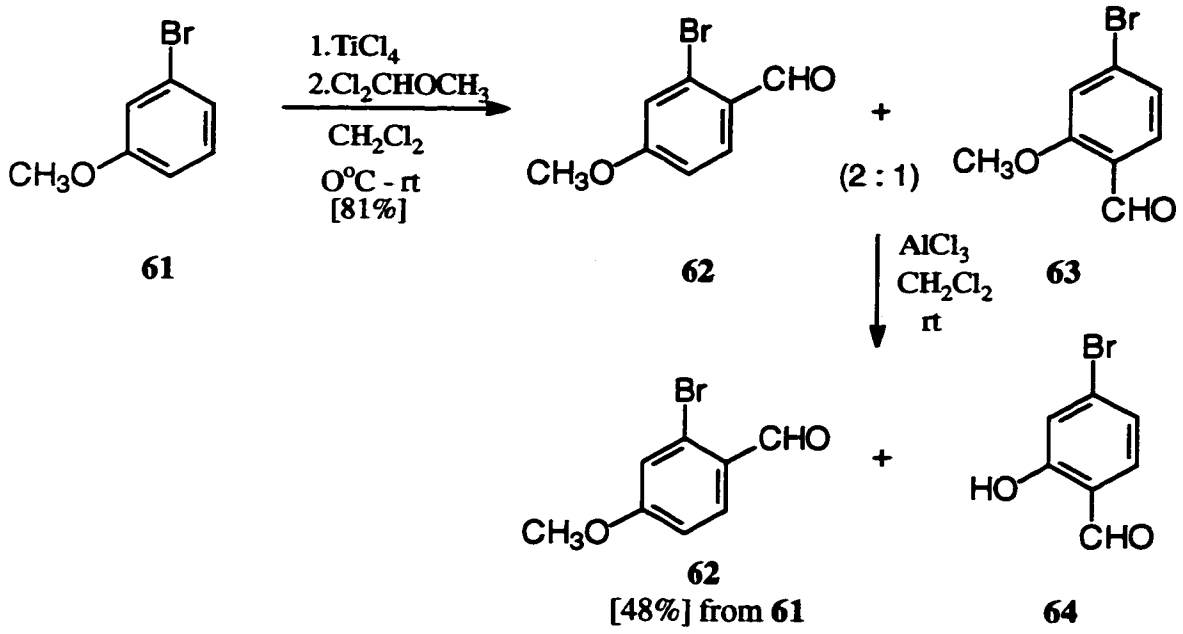


Figure 44. Synthesis of 2-bromo-4-methoxybenzaldehyde

4-Bromo-6-methoxyindole **68** was obtained (Figure 45) by almost the same procedure as the synthesis of 6-methoxyindole **28**. But, since benzaldehyde **62** was not soluble in methanol, THF was used as a co-solvent. Rapoport *et al.*[98] developed a mild, efficient, and regioselective method for the formylation of 4-, 5-, 6-, and 7-lithiated indoles without the need of a protecting group on the indole nitrogen. The potassium salts of indoles were prepared in order to prevent metallation at C-2 and maintain solubility, and have proven to be the most effective species for the metal-halogen exchange reaction of bromoindoles among the investigated bases: *n*-, *sec*-, or *t*-BuLi, CH_3Li, NaH, or CH_3MgI. Martin *et al.*[99] have employed that strategy to prepare several 5-substituted indoles such as formyl, acetyl, thiomethyl, boronic acid, and trimethylstannyl analogues from 5-bromoindole. Therefore, the bromoindole **67** was first converted to the 1-potassio derivative and then subjected to metal-halogen exchange using *t*-BuLi. The metallated species was treated with tri-isopropyl borate to give boronic acid **68** in 73.8% crude yield, which was much better than the reported 44% yield for the preparation of indole-5-boronic acid. In fact, indole-5-boronic acid was resynthesized in 74% yield in this laboratory to confirm the reported reaction conditions.

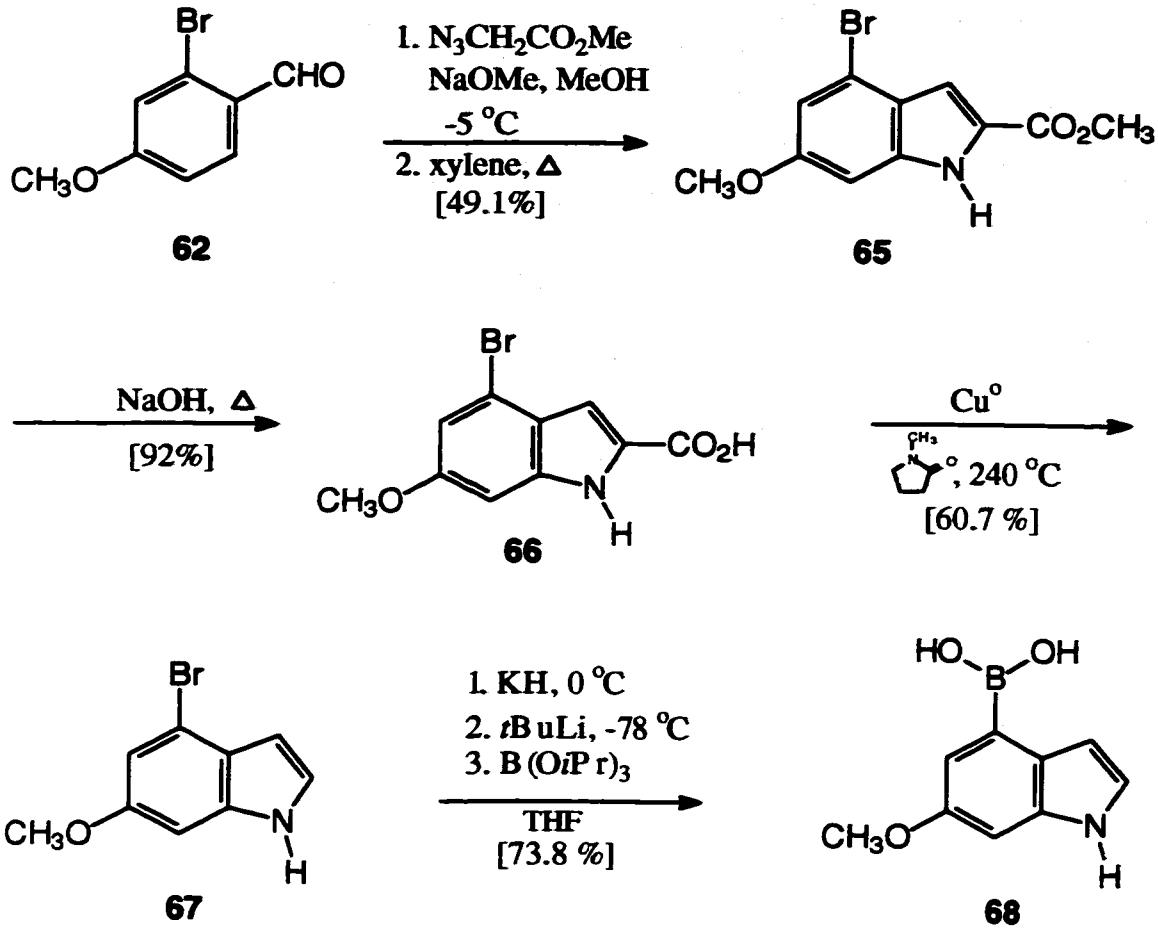


Figure 45. Preparation of 6-methoxyindole-4-boronic acid

4-Hydroxyisoquinoline-3-carboxylic acid **74** was prepared by a literature method.[100,101] The esterification of **74** using trimethylsilyldiazomethane, and subsequent *O*-triflation gave compound **76** (Figure 46).

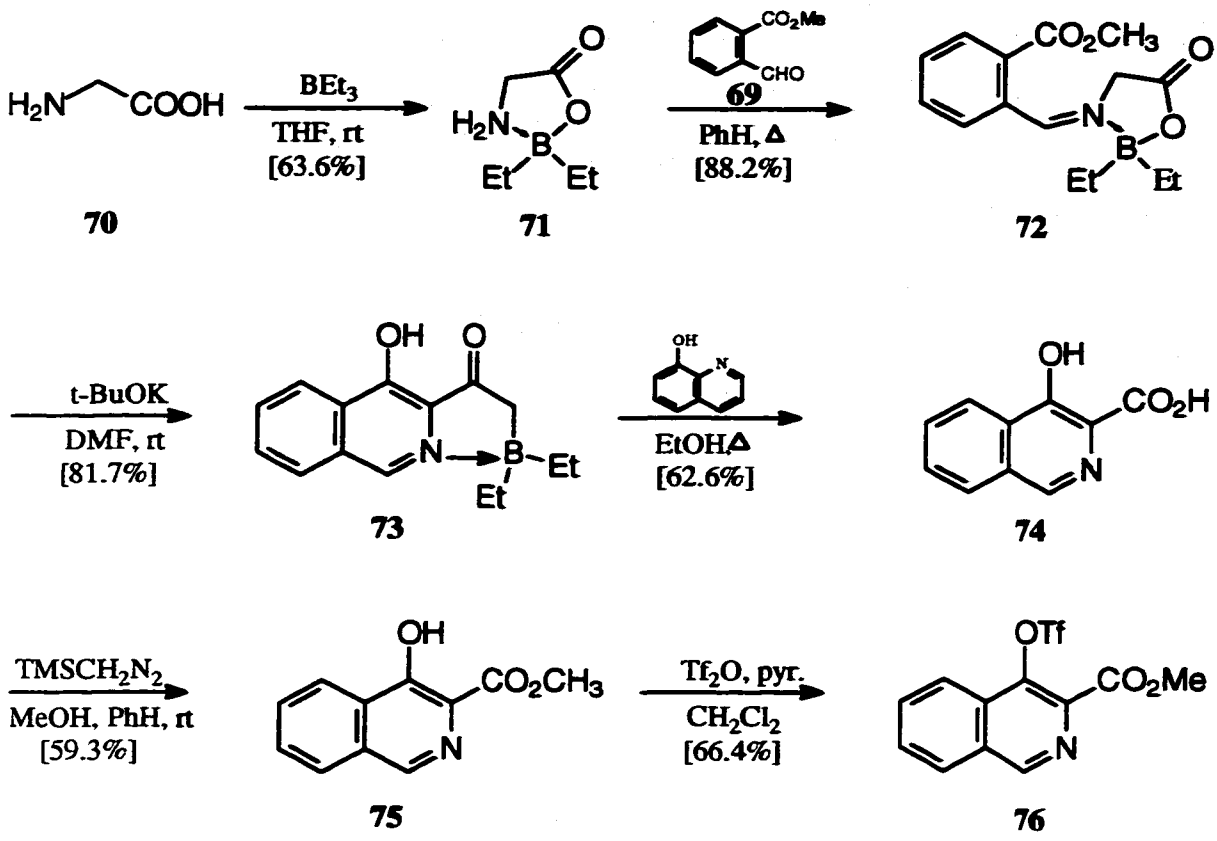


Figure 46. Preparation of isoquinoline-*O*-triflate

The cross-coupling reaction was now accessible *via* a variety of organometallic reagents to provide a fundamentally common synthetic methodology.[102] Many organometallic reagents undergo similar cross-coupling reactions, but much attention has recently been focused on the use of organoboronic acids,[103] because they are convenient reagents, which are generally thermally stable and inert to water and oxygen, thus allowing their handling without special precautions. The cross-coupling reaction of organoboron compounds, which involves the transmetallation to palladium(II) halides as a key step, has been found to proceed smoothly when these were activated with suitable bases and has

proven[104] to be a quite general technique for a wide range of selective carbon-carbon bond formation reactions. The relative reactivity of halides in this reaction decreases in the order I > OTf > Br >> Cl. Regardless of their good reactivity, it has been reported[105] that the coupling using triflate with "wet" or strong bases predominantly led to tars and triflate hydrolysis, which could be limited by using dioxane as a solvent and anhydrous K_3PO_4 as a base. Also, markedly increased yield has been shown by the addition of an O_2-scavenger, 2,6-di-*tert*-butyl-4-methylphenol (BHT), to prevent tar formation attributed to oxidation processes when $PdCl_2$(dppf) was used as a catalyst. The boronic acid **68** and triflate **76** coupled well under the described conditions (Figure 47).

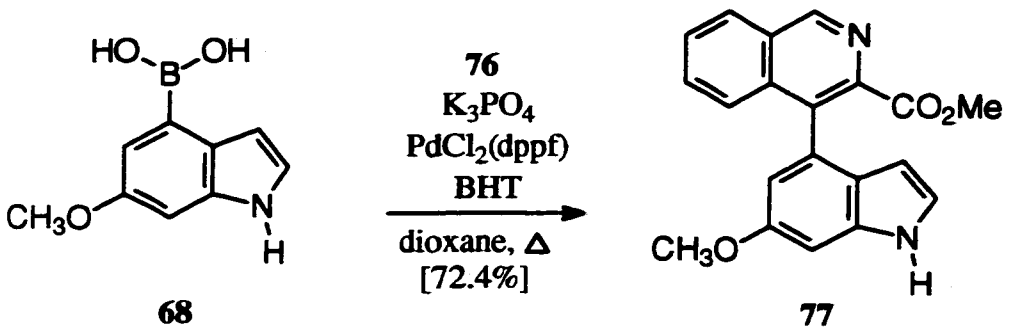


Figure 47. Cross-coupling of indole-boronic acid and isoquinolin-*O*-triflate

Ring closure was attempted at the 3 position of indole **77** and its derivatives. The reduction of isoquinoline was planned after ring closure to avoid extra protection, deprotection steps. Since reduction of a 5,10 double bond of ergolines using $NaCNBH_3$

has been reported[27] to yield trans product (Figure 48), trans-fused benzergoline was anticipated from the reduction of compound **81**.

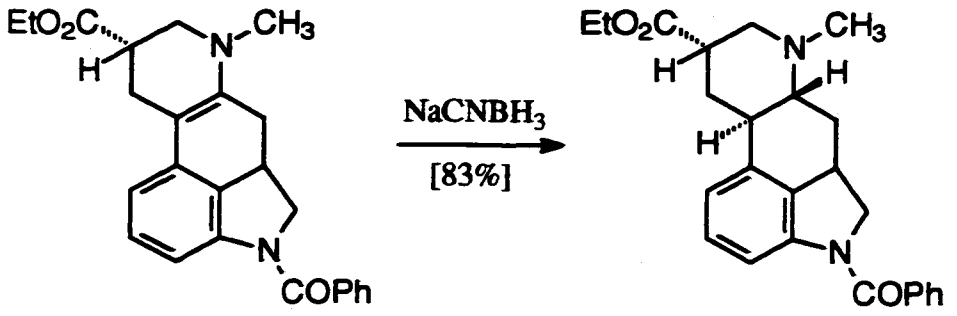


Figure 48. Reduction of 5,10 ergoline using $NaCNBH_3$ by Crider *et al.*[27]

The reaction of 5-, 6- and 7-substituted indoles with *N*-substituted 3-piperidones in methanol using sodium methoxide has been reported to yield 3-substituted indoles in moderate to good yields.[106] Thus, compound **77** was treated with NaOMe, anticipating the benefit of intramolecularity regardless of the low reactivity of the ester (Figure 49). Unfortunately, starting material was primarily recovered after reflux with NaOMe in methanol or toluene for 24 hours. In the presence of Et_3SiH and TFA, the reaction between indoles and aldehydes in CH_2Cl_2 at 0 °C has been reported[107] to result in good yields of C-3 reductively alkylated products. Therefore, the reduction of ester **77** to aldehyde **79** was attempted using DIBAL. Even though the reaction employed only 1 equivalent of DIBAL at -78 °C for 10 min, a significant amount (ca. 30%) of alcohol **80** was obtained along with aldehyde **79** and starting material **77**. The crude mixture of **79** and **80** was treated with TFA/Et_3SiH but several products were formed that were difficult

to identify. Friedel-Crafts reaction conditions for the cyclization at C-3 of indoles are very limited due to the instability of indole under acidic conditions. Nevertheless, PPA has been applied to certain indole components without protecting groups.[108] Thus, PPA reaction of the acid **82** prepared by $Ba(OH)_2$ hydrolysis of **77**, was attempted, resulting again in several products. Due to the low reactivity of the 3-position of isoquinoline and the instability of indole, it appeared from this result that a great deal of effort might be required to optimize conditions for cyclization at C-3 of indole to form ring C.

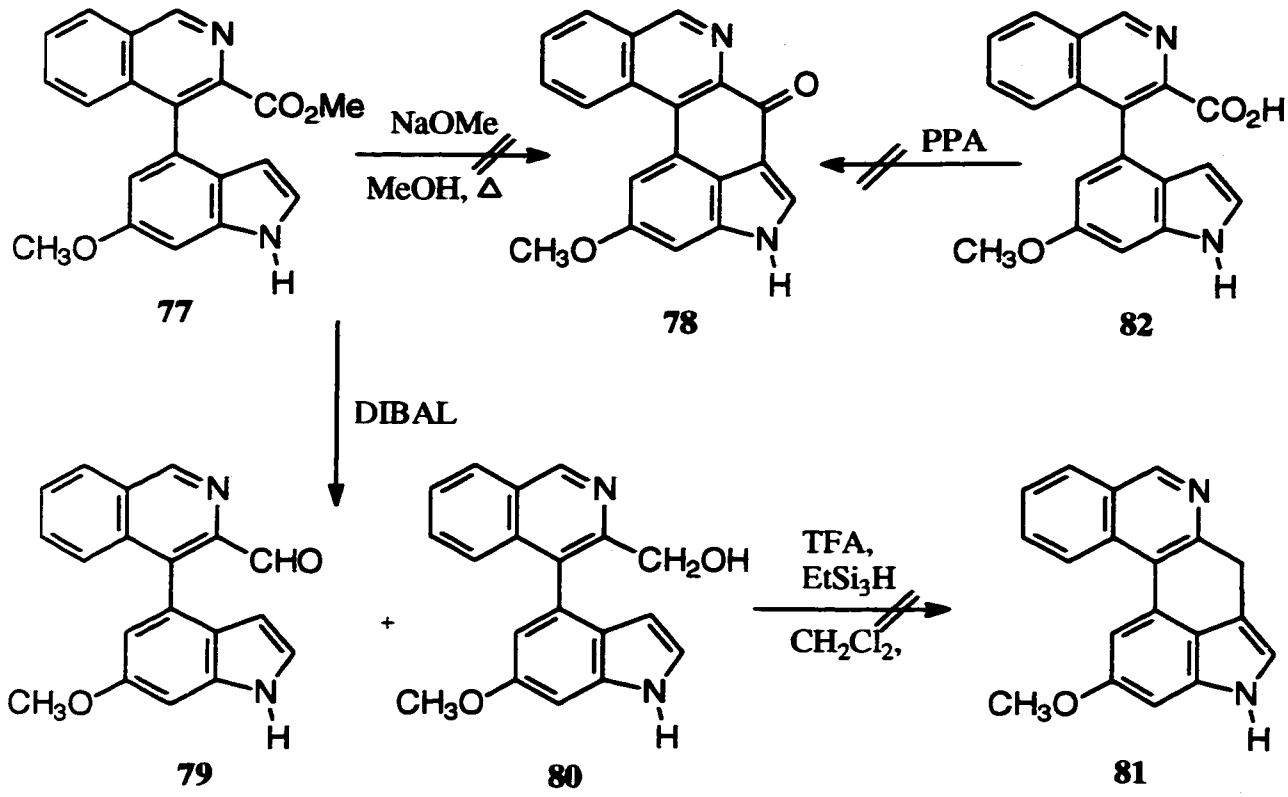


Figure 49. Attempted syntheses for the C-ring closure to form benzergoline (I)

Next, cyclization after reduction of the isoquinoline was examined. Isoquinoline **77** was reduced by $NaCNBH_3$ predominantly to the *cis* isomer **83**, which was confirmed by comparison to the product obtained by catalytic reduction using H_2/PtO_2 (Figure 50). Calculation of minimum energies for both the cis and trans molecules confirmed that the *cis*-fused cyclized compound **87** is more stable than its *trans*-isomer, while the *trans*-isomer is more stable before cyclization. The epimerization of **83** using NaOMe gave only an unidentified very low R_f product (silica, 4% MeOH in CH_2Cl_2). Thus, **83** was protected with a benzyl group by reductive alkylation to afford **84** but in only 54.8% yield. Reflux of **84** in methanol with NaOMe gave **85** (R_f = 0.33, silica, 7:3, hexane/EtOAc, **84**: Rf = 0.31) in 90.0% yield. Surprisingly, the coupling constant between the C-3 and C-4 hydrogens of isoquinoline **85** in the ^1H NMR was 2.1 Hz, smaller than the value of 6.3 Hz for cis **84**. The molecules were modeled, and the dihedral angle (H3-C3-C4-H4) of **85** was calculated as almost 90° (93.8°) affording an explanation for the low coupling constant, while the dihedral angle of **84** was calculated as 47.5°. Attempted PPA cyclization of *cis*-isomer **86** failed, suggested that the cyclization of the *trans*-isomer might also be problematic. Because the *N*-protection yield was not high, cyclization using Friedel-Crafts conditions were not very promising, even though the epimerization proceeded well, so other approaches were next considered. In fact, no synthetic approach involving formation of the 3,4 bond as the last step has been reported for the ergolines.[4]

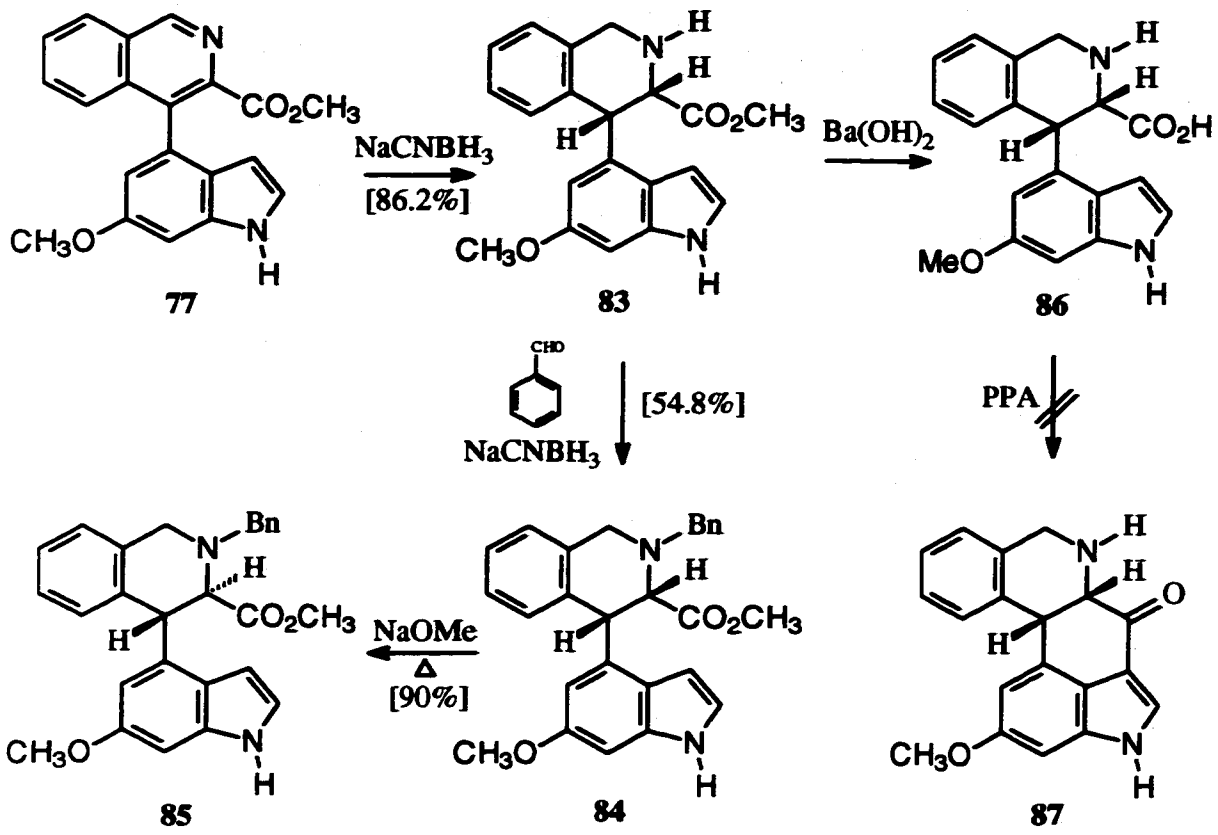


Figure 50. Attempted syntheses on the C-ring closure to form benzergoline(II)

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals, the "Minisci reaction",[109] has been developed as a general reaction in heterocyclic chemistry. Interestingly, it reproduces most aspects of Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity. The homoacylation of heteroaromatic compounds using an acyl radical generated by silver-catalyzed oxidative decarboxylation of α-keto acids by persulfate has been reported.[110]

$$\text{Het-H} + \text{RCOCOOH} + S_2O_8^{2-} \xrightarrow{Ag^+} \text{Het-COR} + CO_2 + 2HSO_4^-$$

In our laboratory, the Minisci reaction was first studied and utilized for the synthesis of an ergoline intermediate by M. A. Doll (personal communication). Synthesis using an intramolecular Minisci reaction was therefore attempted (Figure 51). The boronic acid **68** and commercially available 4-bromoisoquinoline were coupled to form **88** in a 79.5% yield. Oxalyl chloride treatment[111] then gave **89** HCl salt as a yellow powder. Treatment of **89** with wet THF yielded the HCl salt of indole-3-glyoxylic acid **90**, which also contained the HCl salt of unreacted starting material **88**. After converting the crude salt mixture to the free base by treatment with $Ba(OH)_2$ and then CO_2, the **88** was removed by trituration with ether. Compound **90** was thus finally obtained from **88** in a 51.6% yield. Attempted intramolecular cyclization of **90** using Minisci conditions did not lead to the cyclized compound **78**. After careful reinvestigation of the literature, it was found that radical reactions of isoquinoline only occurred at the 1-position, not at the 3-position, while pyridine and quinoline react at both the 2- and 4- positions. The explanation for this was found in resonance structures for isoquinoline, where the aromaticity of the benzenoid ring must be broken to react at the 3-position. It would therefore be difficult to overcome the high transition state energy. No similar problem exists for a radical acylation reaction in the synthesis of ergoline itself. Therefore, it became priority to synthesize another target molecule 13-hydroxyergoline **7**, using the Minisci reaction.

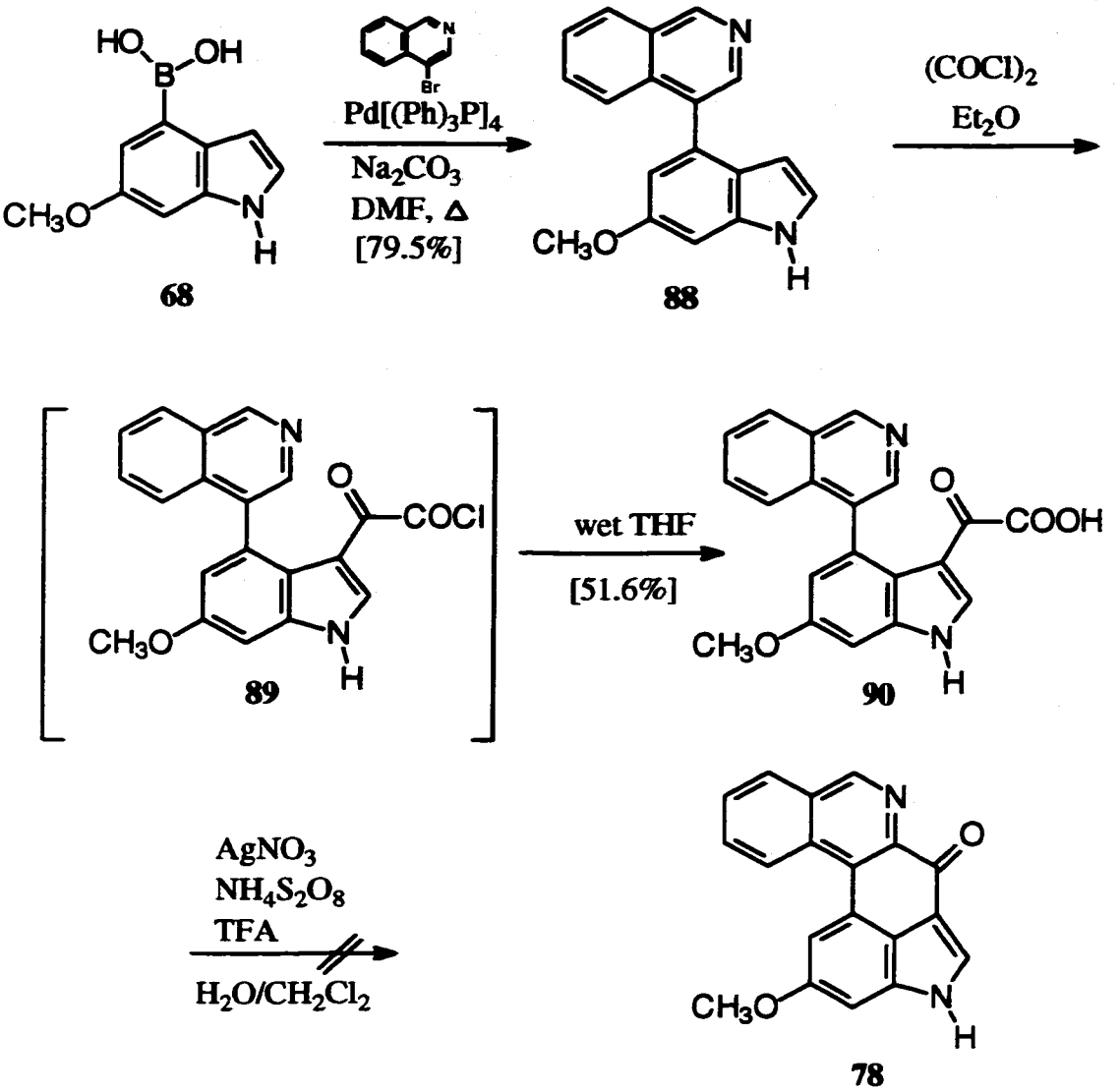


Figure 51. Attempted synthesis of benzergoline *via* a Minisci reaction.

N-6-Methyl-13-hydroxy-9,10-didehydroergoline

Cross-coupling of the boronic acid **68** and 3-bromopyridine gave **91** in 93% yield (Figure 52). Indole-3-glyoxylic acid **93** was prepared by the method described above. In the case of **93**, there are two possibilities for cyclization under Minisci conditions; the 2- and 4-positions of pyridine. It has been postulated[110,112] that the HSAB (hard and soft acids and bases) principle can be extended to free-radical reactions when the polar effect is dominant. Thus, the softness (relatively low ionization potential) of the acyl radicals in polar solvents would promote increased attack at position 4, which is softer than position 2. When acylation of quinoline was carried out with a methyl keto acid in aqueous solution in the presence of CH_2Cl_2 with 1 eq of TFA and 3 eq of persulfate, the ratio of 2- and 4-substitution has been reported as 73:27.[110] The ratio changed to 32:68 when the reaction was carrried out in water alone. Therefore, the intramolecular acylation was performed in a two-phase system (water/CH_2Cl_2) to increase lipophilicity, even though the protonated compound might stay in the aqueous phase. After work up and chromatography, a 24% yield of desired cyclized compound **94** and 44% of undesired **95** were obtained. When sulfuric acid was used instead of trifluoroacetic acid, the ratio of **94**:**95** was approximately 1:2 based on ^{1}H NMR analysis, almost the same result. These two compounds have clearly different chemical shifts and coupling patterns in the ^{1}H NMR spectra, and were easily identified (Table 1). Proton H-9 of compound **94** has a characteristic dd splitting pattern coupled with H-8 (4.7 Hz) and H-10 (7.8 Hz), while proton H-8 (4.3 Hz) and H-10 (8.1 Hz) each appear as a doublet. Proton H-10 of

compound **95** appears as a sharp downfield singlet (9.82 ppm), while the H-7 and H-8 protons are coupled to each other as doublets with a 5.1 Hz coupling constant.

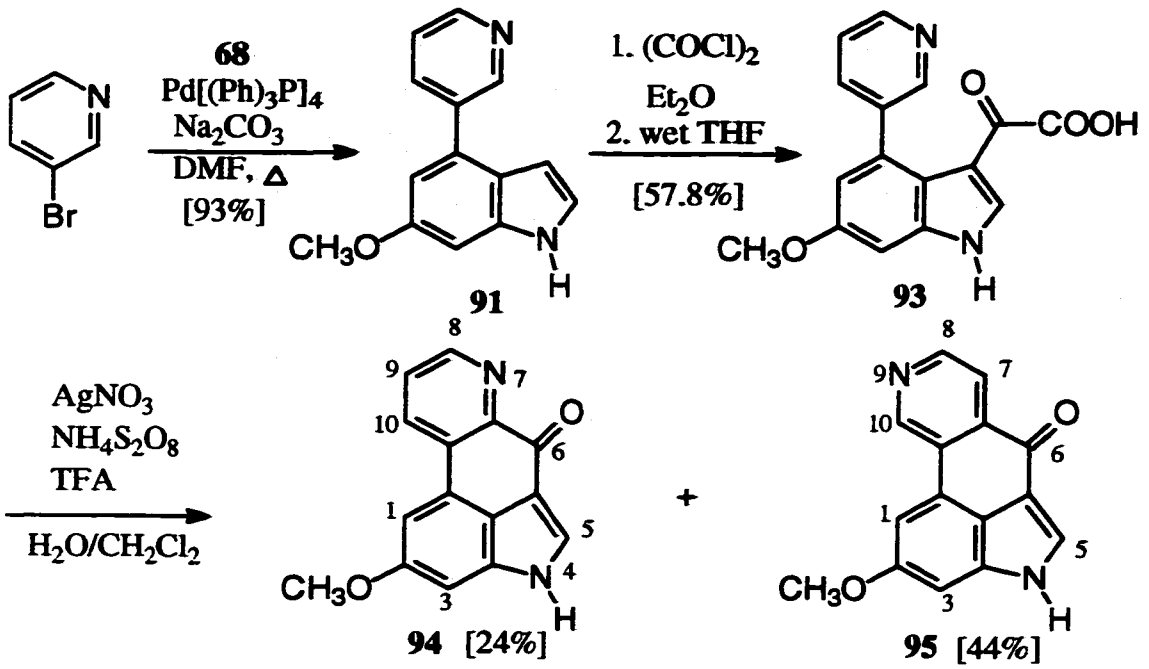


Figure 52. Synthesis of ergolin *via* a Minisci reaction

Table 1. ^{1}H NMR (DMSO-d_6) spectra of indoloquinoline **94** and indoloisoquinoline **95**

	chemical shift (ppm)		splitting		coupling constant (Hz)	
	94	**95**	**94**	**95**	**94**	**95**
H-1	6.42	7.26	d	d	1.9	1.3
H-3	6.59	7.94	d	d	1.9	1.7
NH-4	11.08	12.7	bs	bs		
H-5	8.73	8.47	s	s		
H-7		8.14		d		5.1
H-8	8.60	8.77	d	d	4.3	5.1
H-9	7.47		dd		4.7, 7.8	
H-10	7.96	9.82	d	s	8.1	

The next consideration was to block the 4-position of pyridine with a carboxylate, which might even increase the nucleophilic reactivity through an electron withdrawing effect. Therefore, the method for decarboxylation of pyridinecaboxylic acids was investigated. It was found that pyridinecarboxylic acids are relatively easily decarboxylated in the order of 2- > 4- > 3-carboxylic acid,[113] because they form a zwitterion intermediate, leading to thermal decarboxylation without a catalyst or a base. Picolinic acid especially can lead to a cyclic transition state as well as a zwitterionic intermediate. After loss of CO_2, pyridine forms an intermediate ylide, which can be trapped with an electrophile, a sequence known as the Hammick reaction.[114,115] The Hammick reaction is a general synthesis of carbinols by decarboxylation of certain heterocyclic carboxylic acids in the presence of carbonyl compounds. This method appeared well suited for the synthesis of ergoline **7**.

As a preliminary experiment, the Hammick reaction of picolinic acid and 3-indolecarboxaldehyde was not successful, probably due to the low electrophilicity of the aldehyde. *N*-Tosyl-3-indolecarboxaldehyde **96** (1 eq) was coupled, however, with pyridine in 3-nitotoluene to form **97** in a 20% crude yield (Figure 53)

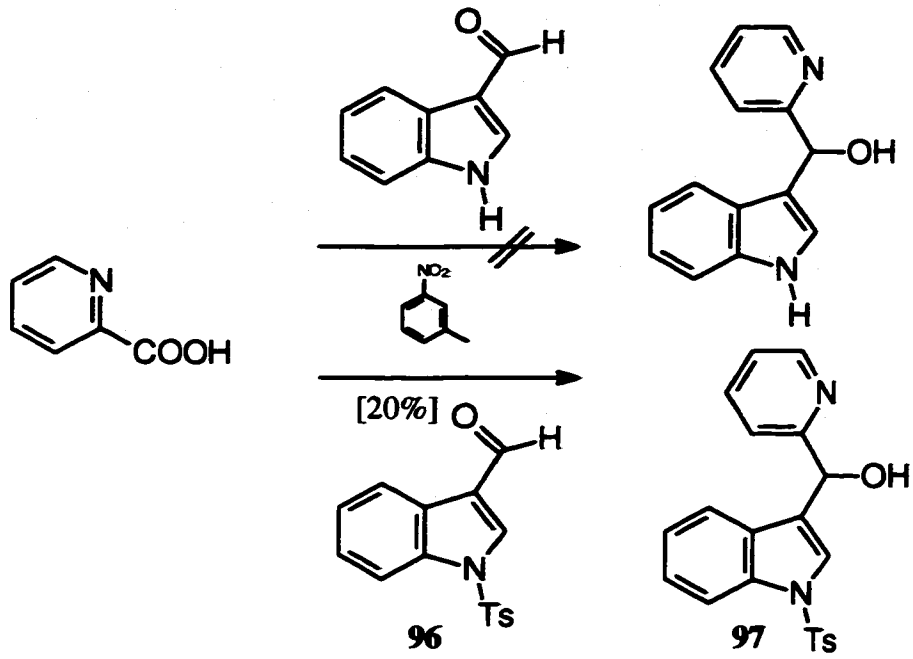


Figure 53. A Hammick reaction of picolinic acid and 3-indolecaboxaldehyde.

Thermal decomposition of methoxypyridine-2-carboxylic acid in benzaldehyde has been described as leading to two products, the corresponding methoxy-2-pyridyl phenyl carbinol and the methoxypyridine.[116] The formation of two products is shown in Figure 54. The slow or rate-determining step a results in the formation of reactive intermediate I which then reacts in subsequent fast or product-determining steps b and c. The product ratio, carbinol to methoxypyridine, reflects steps b and c. If excess aldehyde **96** was used, the coupled yield should be increased. Step c involves only a proton transfer (known as a fast process), while step b involves reaction of I with benzaldehyde. For step b to be faster than step c, the benzaldehyde molecules (which are in excess) must occupy favorable positions around intermediate I. According to this postulation, the yield of

intramolecular trapping of yildes with aldehyde could be markedly increased, an attractive possibility for the present work.

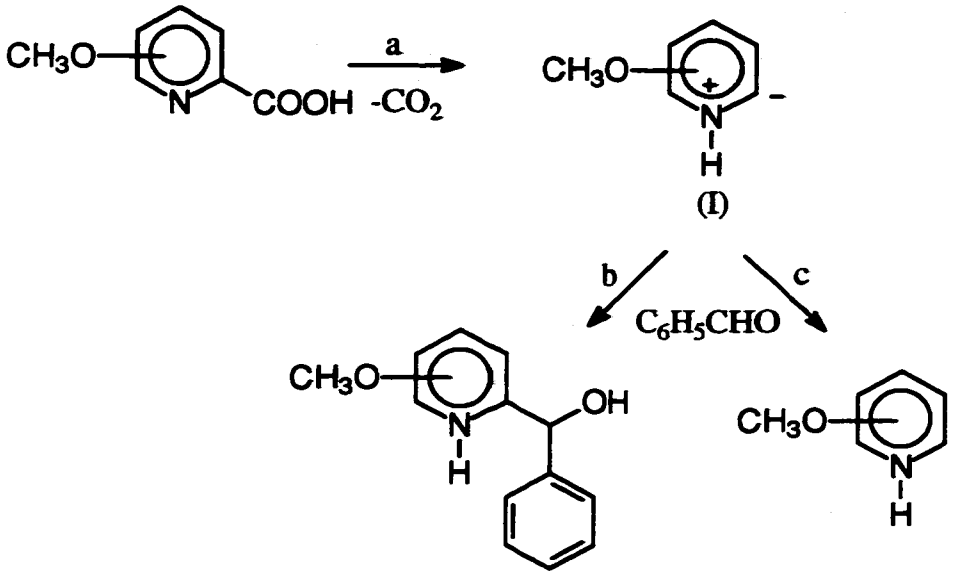


Figure 54. Suggested mechanism for the formation of two products by a Hammick reaction (Brown *et al.*[116])

Figure 55 shows another route to synthesize ergolines *via* a Hammick reaction. 3-Iodomethylpicolinate has been prepared from picolinic acid in 4 steps.[117] The Suzuki-coupling should not be problematic, and then formylation is anticipated to give a good yield of 4-(3-pyridyl)-3-indolecarboxaldehyde. The Vilsmeier reaction of 4-(3-pyridyl)-indole has been reported in 92% yield.[18] After *N*-tosyl protection and hydrolysis of ester **98**, an intramolecular Hammick reaction was therefore planned to obtain compound **101**.

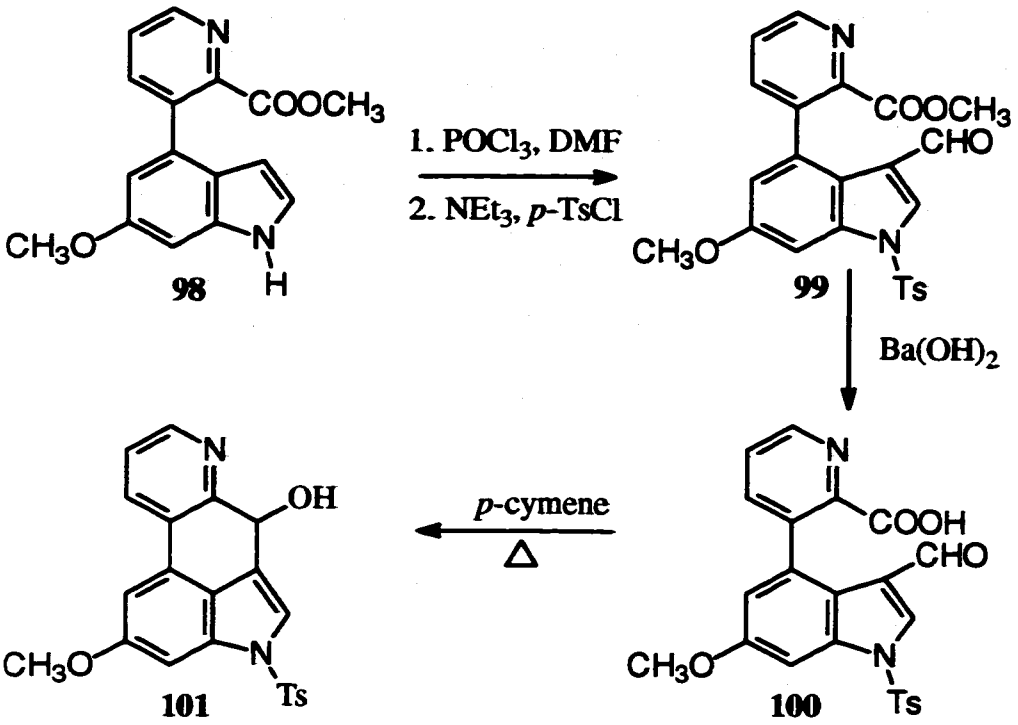


Figure 55. Synthetic plan for ergoline *via* a Hammick reaction

On the other hand, coupling of 3-iodomethylnicotinate[117] with boronic acid **68** and formation of the glyoxylic acid **103**, then a subsequent Minisci reaction should lead to a single cyclized product **104** (Figure 56). Following hydrolysis of ester **104** to the acid **105**, thermal decarboxylation will yield compound **94**. By comparing the overall yield and convenience of the reactions, the best way to synthesize **7** would be decided.

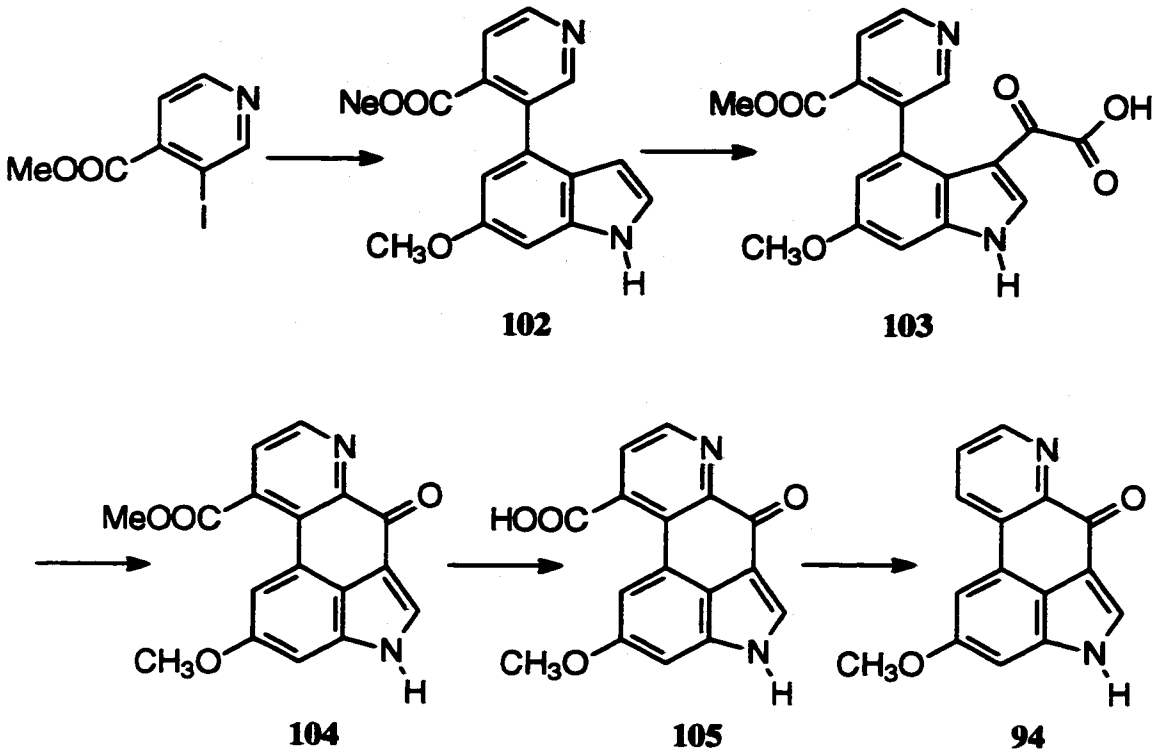


Figure 56. Synthetic plan for ergoline *via* a Minisci reaction

To plan the synthesis of target molecule **7** after cyclization (Figure 57), a literature search and preliminary experiments were accomplished. LAH will easily remove the *N*-tosyl protecting group of **101**,[118] and concomitantly reduce the ketone **94** or the alcohol **101** to the methylene. As a preliminary experiment (Figure 58), the reduction of 3-(2-pyridyl)-indolecarbinol **109** using LAH was carried out and furnished an almost quantitative yield of the corresponding methylene **110**. In a literature report,[15] a 6-dihydroindoloquinoline derivative was mesylated and reduced to the 9,10-didehydroergoline derivative using $NaBH_4$, a method applicable to the preparation of **108** from **106**, which following *O*-demethylation would lead to the target molecule **7**.

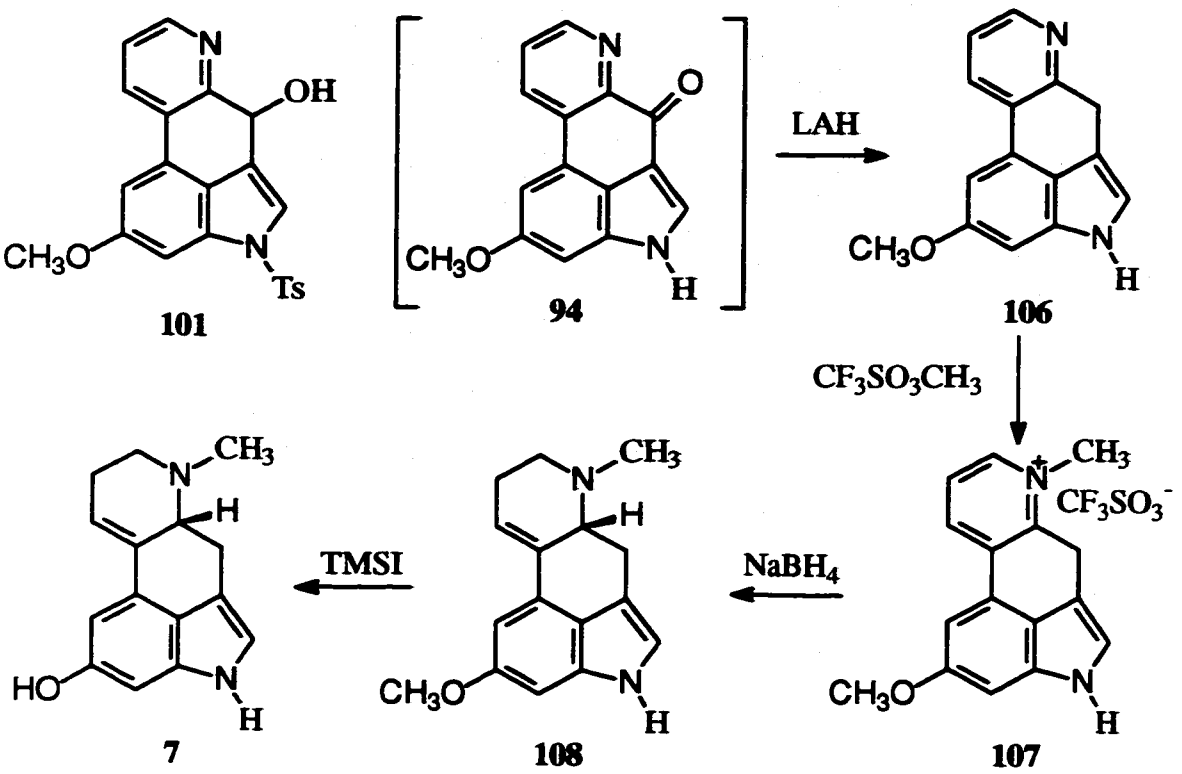


Figure 57. Synthetic plan for 13-hydroxy-9,10-didehydroergoline

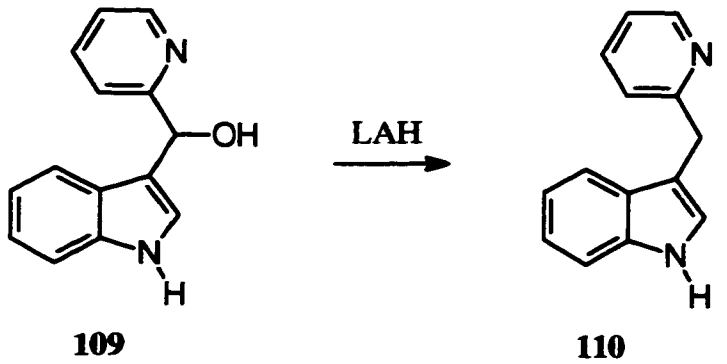


Figure 58. Reduction of 3-(2-pyridyl)-indolecarbinol by LAH

In reviewing the benzergoline project, the Hammick reaction was considered. As described above, the attempted cyclization of isoquinolinecarboxylic acid **82** with PPA at 80 °C yielded several products (Figure 49). Protonated pyridinium, however, has been reported[119] to lose CO_2 at 60 °C, and it appeared likely that a decarboxylation reaction could be employed. It was concluded that benzergolines **1**, **2**, and **3** could probably be synthesized *via* a Hammick reaction (Figure 59).

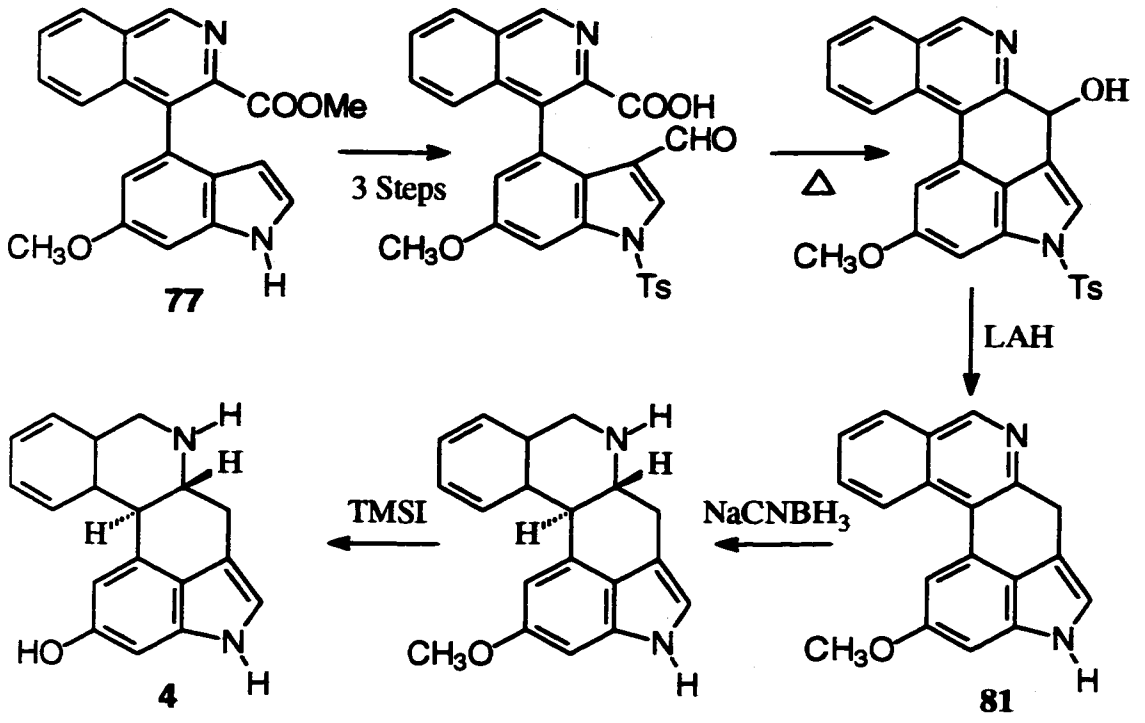


Figure 59. Synthetic plan for 2-hydroxybenzergoline *via* a Hammick reaction.

CONCLUSION

Three types of ring A-substituted ergolines presented in Figure 19 were designed and their syntheses were attempted *via* several synthetic strategies. 12-Methoxyergolines were synthesized and are currently being assayed for *in vitro* activity at serotonin receptors. The synthesis of 12-methoxyergolines included development[47] of a new procedure for the preparation of starting material, 8-methoxy-β-tetralone. A Leimgruber-Batcho indole ring closure was employed as the last step, through a tricyclic benzo[*f*]quinoline. This circumvents the problem of protecting the indole nucleus, since it is well known that the pyrrole ring of the ergoline ring structure is the most sensitive part.

Initial attempts to prepare the tricyclic *N*-tosyl-7-methoxy-4-keto-1,2,2a,3,4,5-hexahydrobenz[*c,d*]indole **38** as an intermediate for the synthesis of 2-hydroxy-benz-ergolines were not successful. Both the homoacylation of 6-methoxyindole-3-acetic acid derivatives and the Friedel-Crafts reaction of 6-methoxyindole-3-propionic acid derivatives were attempted to effect ring closure into the 4-position of 6-methoxyindole under various reaction conditions, but none of those provided any significant yield of product.

While the 4-position of 6-methoxyindole is not favorable for electrophilic attack, nucleophilic substitution of *N*-triisopropylsilyl protected 6-methoxyindole-chromium tricarbonyl complex **51** occurred regioselectively at the 4-position. Due to low

nucleophilicity of our synthons, however, attempts to introduce desired functionality at the 4-position failed.

New synthetic approaches to assemble two synthons; indole, and isoquinoline or pyridine, were attempted to prepare 2-hydroxybenzergolines **4**, **5**, and **6**, and 13-hydroxyergoline **7**. 6-Methoxyindole-4-boronic acid **68** was prepared in good yield by a metal-halogen exchange reaction from 4-bromo-6-methoxyindole **67** without a protecting group, and was then coupled efficiently with isoquinoline or pyridine halides under Suzuki-cross coupling condition.

After cross coupling, several trials to form ring C were unsuccessful. Finally, a Minisci reaction with 6-methoxy-4-(3-pyridyl)indole **91** using an acyl radical, an approach previously studied in our laboratory, yielded cyclized products **94** and **95**. To avoid undesired cyclization at the 4-position of pyridine, it was proposed to block that position with carboxylate, which might later be relatively easily removed.

Utilization of an intramolecular Hammick reaction was also examined as a method to synthesize both 2-hydroxybenzergolines and 13-hydroxyergoline with promising results. The approach *via* a Minisci or a Hammick reaction may provide a new entry to the total synthesis of ergolines with a substituent in ring A.

EXPERIMENTAL

All reactions were performed in standard glass apparatus under an inert atmosphere of argon or nitrogen. Starting materials, solvents and reagents were purchased commercially, except where noted. Dry THF, diethyl ether, and benzene were distilled from sodium benzophenone ketyl and pyrrolidine was distilled from sodium before use. Dry methanol and dichloromethane were distilled from CaH_2. All ^1H NMR spectra were recorded on a Bruker ARX 300 MHz instrument. Chemical shifts are reported in δ values (parts per million, ppm) relative to an internal standard of trimethylsilane (TMS) in $CDCl_3$, except where noted. Abbreviations used to report NMR peaks are as follows: bs = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet, td = triplet of doublets. Melting points were determined with a Thomas-Hoover Meltemp apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Baker-Flex silica gel 1B2-F plastic plates. Chemical ionization mass spectra (CIMS) and fast atom bombardment spectra were determined on the Purdue University Department of Medicinal Chemistry and Molecular Pharmacology's Finnegan 4000 quadrupole mass spectrometer. Elemental analyses were obtained from the Purdue Microanalysis Laboratory and all of the results are within 0.4% of calculated values.

8-Methoxy-β-tetralone

Method A.

1,7-Dimethoxynaphthalene (9).[49,121] 1,7-Dihydroxynaphthalene (**8**) (40 g, 0.24 mol) was added to 2N NaOH (240 mL) and stirred for 20 min at 0 °C. To the solution was added dimethyl sulfate (50.4 mL, 0.53 mol) over 15 min via a dropping funnel, and the mixture was stirred for 20 min at 0 °C. The reaction mixture was poured into 2N NaOH (120 mL), and additional dimethyl sulfate (25.6 mL, 0.27 mol) was added at 0 °C. After completion of the addition, the ice/water bath was removed, and the reaction was continuously stirred for an additional 30 min at rt, and then heated at reflux for 30 min, cooled, and extracted with CH_2Cl_2 (2 x 120 mL). The organic extract was washed with 2N NaOH (2 x 120 mL), brine (120 mL), and water (120 mL), dried ($MgSO_4$), was filtered, and concentrated under reduced pressure. The resulting purple liquid was purified by Kugelrohr distillation (bp 105-110 °C, 0.2 mm Hg) [Lit.[121] 170 °C, 20 mm Hg] to give **9** (42.3 g, 90%) as a colorless liquid.

8-Methoxy-3,4-dihydronaphthalen(1H)-2-one (10).[49,121] 1,7-Dimethoxynaphthalene (**9**) (20.0 g, 0.106 mol) in absolute ethanol (220 mL) was placed in a 500 mL three necked flask equipped with mechanical stirrer, reflux condenser, and nitrogen line. The solution was heated to reflux, and sodium (29.24 g, 1.27 mol) was added in small pieces over 30 min, followed by additional absolute ethanol (50 mL). The reaction was heated at reflux for 40 min, and cooled to rt. Water (120 mL) was cautiously added to the mixture

with stirring, and the volatile components were then removed under reduced pressure. Water (75 mL) was added to the residue, and the layers were separated. The aqueous lower layer was extracted with dioxane (3 x 50 mL), and combined with the oily upper layer. The organic extract was placed into a flask equipped with reflux condenser, and 5N HCl (200 mL) was added. The solution was heated in a steam bath with stirring for 30 min, and then cooled to rt. The layers were separated, and the upper aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). A saturated $NaHSO_3$ solution (20 mL) was added to the organic extract, and the mixture was stirred overnight. The bisulfite adduct was formed as a white solid, and collected by filtration. The solid was added to a saturated $NaHCO_3$ solution (35 mL), and the mixture was extracted with CH_2Cl_2 (3 x 50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an oil. The resulting oil was crystallized from petroleum ether to afford colorless needles (7.2 g, 37.3%): mp 59-60 °C [Lit.[121] mp 59.5-61 °C]; ^{1}H NMR δ 7.18 (dd, 1, ArH, J = 7.8 and 7.8 Hz), 6.83 (d, 1, ArH, J = 7.5 Hz), 6.76 (d, 1, ArH, J = 8.1 Hz), 3.80 (s, 3, OCH_3), 3.5 (s, 2, $ArCH_2CO$), 3.0 (t, 2, $ArCH_2$, J = 6.7 Hz), 2.5 (t, 2, $COCH_2$, J = 6.7 Hz).

Method B.

2-Bromoacetylchloride (12).[122] Oxalyl chloride (44.4 g, 350 mmol) was added slowly with stirring to a 0 °C solution of 2-bromophenylacetic acid (30 g, 140 mmol) in CH_2Cl_2 (90 mL), containing a few drops of dry DMF. The reaction mixture was stirred at rt for

6 h. The solvent and excess oxalyl chloride were removed *in vacuo* to give a light yellow oil, which was used in next step without further purification.

8-Bromo-3,4-dihydronaphthalen(1H)-2-one (13).[122] A 2 L resin kettle reactor equipped with mechanical stirrer, dropping funnel and low temperature thermometer, and containing $AlCl_3$ (69 g, 520 mmol) in CH_2Cl_2 (1200 mL), was cooled to -5 °C in an ice/salt bath with vigorous mechanical stirring. The crude acid chloride **12** in CH_2Cl_2 (120 mL) was added dropwise, and then ethylene was introduced for one hour through a gas inlet tube. Stirring was continued for an additional hour at -5 °C. The reaction was poured over ice (2000 g), stirred vigorously for a few minutes, and set aside until the ice melted. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic extract was filtered through a pad of Celite, washed with 2N HCl (2 x 300 mL) and a saturated $NaHCO_3$ solution (2 x 300 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting oil was purified by Kugelrohr distillation (bp 86-95 °C, 0.01 mm Hg), and then crystallized from petroleum ether to give **13** as a white solid (21 g, 68% from 2-bromophenylacetic acid): mp 74-75 °C [Lit.[122] mp 75 °C]; ^{1}H NMR δ 7.30 (d, 2, ArH, J = 6.8 Hz), 7.19 (d, 1, ArH, J = 7.5 Hz), 7.09 (dd, 1, ArH, J = 7.7 and 7.7 Hz), 3.67 (s, 2, $ArCH_2CO$), 3.10 (t, 2, J = 6.8 Hz, $ArCH_2$), 2.60 (t, 2, J = 6.8 Hz, $COCH_2$).

8'-Bromo-3'4'-dihydrospiro-[1,3-dioxolane-2,2'(1H)-naphthalene] (14). A solution of **13** (18 g, 80 mmol), ethylene glycol (9.9 mmol, 160 mmol) and *p*-TsOH (1.3 g,

6.7 mmol) in benzene (350 mL) was heated at reflux for an hour under nitrogen using a Dean-Stark apparatus for water removal. The cooled solution was diluted with diethyl ether, and washed with a saturated $NaHCO_3$ solution (2 x 200 mL), dried (Na_2SO_4), filtered, and was concentrated *in vacuo* to give **14** as an oil (19.6 g, 91%) which was not purified further: ^{1}H NMR δ 7.4 (dd, 1, ArH, J = 7.8 Hz), 7.1 (d, 1,ArH, J = 7.4 Hz), 7.0 (d, 1, ArH, J = 7.7 Hz), 4.0 (m, 4, OCH_2CH_2O), 3.0 (s.2, $ArCH_2CO$), 2.9 (t, 2, $ArCH_2$, J = 7.7 Hz), 1.94 (t, 2, $COCH_2$, J = 7.8 Hz).

8'-Methoxy-3'4'-dihydrospiro-[1,3-dioxolane-2,2'(1H)-naphthalene] (15). To a flame dried two neck reaction flask (250 mL) were added **14** (19 g, 70 mmol), a 5.0 M solution of sodium methoxide in methanol (220 mmol, 45 mL), ethyl acetate (3.64 g, 28 mmol) and cuprous bromide (1.43 g, 10 mmol). The reaction mixture was heated at reflux for 5 h, cooled to rt, and then the volatile components were removed under reduced pressure. Water (800 mL) was added to the residue, which was then extracted with CH_2Cl_2 (3 x 300 mL). The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a pale yellow oil **15** (13 g, 86%): ^{1}H NMR δ 7.1 (dd, 1, ArH, J = 7.8 and 7.8 Hz), 6.73 (d, 1, ArH, J = 7.7 Hz), 6.64 (d, 1, ArH, J = 8.1 Hz), 4.0 (m, 4, OCH_2CH_2O), 3.77 (s, 3, OCH_3), 2.98 (t, 2, $ArCH_2$, J = 6.5 Hz), 2.8 (s, 2, $ArCH_2CO$), 1.9 (t, 2, $COCH_2$, J = 6.7 Hz).

8-Methoxy-3,4-dihydronaphthalen(1H)-2-one (10).[49,121] Ketal **15** (13 g, 59 mmol) was heated with stirring at 100 °C in 50% aqueous acetic acid (400 mL) for 3 h. The reaction

mixture was quenched with water (400 mL), and extracted with ether (3 x 200 mL). Organic extract was washed with 10% NaOH, and water, dried (Na_2SO_4), and filtered, concentrated *in vacuo*. The resulting oil was purified by Kugerohr distillation, and crystallized from petroleum ether to afford **10** as white needles (9.5 g, 92%).

Trans-10-methoxy-7-nitro-octahydrobenzo[*f*]quinoline

10-Methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (17).[46] To a solution of 8-methoxy-2-tetralone (**10**) (9.5 g, 0.054 mol), *p*-TsOH (80 mg) in benzene (100 mL) was added freshly distilled pyrrolidine (5.76 g, 0.081 mol) in benzene (40 mL) dropwise *via* a dropping funnel. The mixture was heated at reflux in a Dean-Stark apparatus for 5 h. After cooling, all volatile components were removed under reduced pressure. The resulting enamine **16** was heated at 80 °C, then acrylamide (11.5 g, 0.162 mol) was added and the reaction was stirred at 80 °C for 2 h. The temperature was increased to 130 °C, and the mixture was stirred at this temperature for 25 min to polymerize excess acrylamide. To the hot mixture, water (40 mL) was added, which was stirred vigorously for 20 min. After standing at rt, the water was decanted and the yellow solid was purified by chromatography (silica, 1:1 hexane/EtOAc). The resulting off-white solid was recrystallized from ethyl acetate to give white needles (4.72 g, 38%): mp 178-179 °C (EtOAc) [Lit.[46] mp 182 °C (acetone)]; ^{1}H NMR δ 7.55 (b, 1, NH), 7.15 (dd, 1, ArH, J = 7.5 and 7.5 Hz), 6.78 (d, 2, ArH, J = 7.8 Hz), 3.80 (s, 3, OCH_3), 2.98 (t, 2, $ArCH_2$, J = 7.8 Hz), 2.81 (t, 2, CH_2, J = 7.5 Hz), 2.54 (t, 2, CH_2, J = 7.5 Hz), 2.26 (t, 2, CH_2, J = 7.5 Hz); CIMS 230 (MH^+).

***Trans*-10-methoxy-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (18).**[46] A mixture of enamide **16** (4.58 g, 0.02 mol) and triethylsilane (6.98 g, 0.06 mol) in dry CH_2Cl_2 (15 mL), was stirred at rt for 10 min., and cooled to 0 °C in an ice bath. Trifluoroacetic acid (34.2 g, 0.3 mol) was added dropwise through a dropping funnel at 0 °C with stirring, and the mixture was continuously stirred at rt overnight. The volatile components were removed under reduced pressure to afford an oily residue, which was taken up into CH_2Cl_2 (25 mL), and carefully neutralized with saturated $NaHCO_3$. The layers were separated and the organic layer was washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give an off-white solid (4.3 g, 93.5% crude yield). The NMR spectrum showed an approxamately 7:3 ratio of trans:cis compounds, which were difficult to separate by chromatography or crystallization, and then used for the next step without separation. Crystallization from ether/hexane gave white needles with about the 25% of the cis isomer: mp 218-219 °C (Lit.[46] mp 219.5-221.5 °C); ^{1}H NMR ($CDCl_3$) δ 7.13 (dd, 1, ArH, J = 8.1 and 8.1 Hz), 6.71 (d, 2, ArH, J = 8.1 Hz), 3.83 (s, 3, OCH_3), 3.63 (m, 1, NCH), 3.34 (m, 1, ArCH), 2.84 (m, 2, $ArCH_2$), 2.51 (m, 2, CH_2CO), 2.21 (m, 1, $ArCHCH_2$), 1.93 (m, 2, $ArCH_2CH_2$), 1.71 (m, 1, $ArCHCH_2$); CIMS 232 (MH^+).

***Trans*-10-methoxy-7-nitro-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one (19).** A mixture of 70% nitric acid (90 mL) and sodium nitrite (1.15 g, 16.67 mmol) was cooled to 0 °C, and **18** (3 g, 13.08 mmol, containing approximately 2.1 g of trans compound) was added portionwise over 30 min. After stirring at rt overnight, the reaction mixture was

poured over ice, neutralized with NH_4OH, and extracted with CH_2Cl_2. The organic extract was washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a yellow solid (2.56 g, 71.5% of total crude nitration). Flash chromatography (silica, 1:1:0.2 hexane/EtOAc/MeOH) separated **19** (1.34 g, 37.5%) and other isomers. Compound **19** was crystallized from methanol as pale yellow needles: mp 228-230 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 1, ArH, J = 9.3 Hz), 6.81 (d, 2, ArH, J = 9.0 Hz), 6.03 (bs, 1, CONH), 3.93 (s, 3, OCH_3), 3.65 (m, 1, CH), 3.38 (m, 1, CH), 3.16 (ddd, 1, $ArCH_2$, J = 2.4, 5, and 18.5 Hz), 2.99 (m, 1, $ArCH_2$), 2.47 (m, 1, CH_2CO), 2.38 (ddd, 1, CH_2CO, J = 2, 4.5, and 14 Hz), 2.16 (m, 1, CH_2), 2.02 (m, 1, CH_2), 1.86 (m, 1, CH_2), 1.70 (m, 1, CH_2); CIMS 277 (MH^+); Anal ($C_{14}H_{16}N_2O_4$) C, H, N.

***Cis*-10-methoxy-7-nitro-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one.** MP 263-266 °C; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 1, ArH, J = 9.0 Hz), 6.79 (d, 2, ArH, J = 9.0 Hz), 6.18 (b s, 1, CONH), 3.91 (s, 3, OCH_3), 3.44 (t, 1, ArCH, J = 7.5 Hz), 3.23 (m, 1, $ArCH_2$), 3.06 (m, 1, $ArCH_2$), 2.80 (t, 1, NCH, J = 7.2 Hz), 2.61 (m, 2, CH_2CO), 1.99 (m, 2, CH_2), 1.56 (m, 2, CH_2).

***Trans*-10-methoxy-9-nitro-1,4,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(2*H*)-one.** MP 198-201 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 1, ArH, J = 8.7 Hz), 6.95 (d, 2, ArH, J = 8.4 Hz), 6.40 (bs, 1, CONH), 3.92 (s, 3, OCH_3), 3.69 (m, 1, CH), 3.36 (m, 1, CH), 2.90 (m, 2, $ArCH_2$), 2.51 (m, 2, CH_2CO), 2.21 (m, 1, CH_2), 2.01 (m, 2, CH_2), 1.79 (m, 1, CH_2).

***Trans*-10-methoxy-7-nitro-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (20).** To a flame-dried 500 mL three necked flask, the lactam **19** (1.0 g, 3.6 mmol) was dissolved in dry THF (150 mL), and cooled to 0 °C. BH_3 (15 mL, 1M in THF) was added dropwise to the reaction, which was then heated at reflux for 7 h. After cooling, methanol (50 mL) was carefully added to the mixture, while vigorous gas evolution was observed, followed by heating at reflux overnight. After cooling, the volatile components were removed *in vacuo*, and water (150 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting brown oil was dissolved in 1N HCl (100 mL), the acidic solution was washed with ether (2 x 50 mL), and then basified with NH_4OH. The basic solution was extracted with CH_2Cl_2 (3 x 50 mL), and the extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a brown solid (601 mg, 64%). Methanolic HCl (1 M, 3 mL) was added to the free base, and the solution was concentrated under reduced pressure. The resulting salt was crystallized from EtOH/Et_2O to give a yellow solid (529 mg, 49%): mp 289-291 °C (dec); ^{1}H NMR ($CDCl_3$, free base) δ 7.85 (d, 1, ArH, J = 9.0 Hz), 6.72 (d, 1, ArH, J = 9.0 Hz), 3.87 (s, 3, OCH_3), 3.18-3.07 (m, 4, ArCH, NHCH, $ArCH_2$), 2.83 (dd, 2, $NHCH_2$, J = 3.5 and 10.7 Hz), 2.34 (m, 1, CH_2), 2.03 (m, 1, CH_2), 1.74 (s, 1, NH), 1.70-1.61 (m, 3, CH_2), 1.28 (m, 1, CH_2); HR CIMS for $C_{14}H_{18}N_2O_3$ 263.1396 found 263.1387 (MH^+).

12-Methoxyergolines

Tripiperidinomethane (21) (TPM).[64] A mixture of piperidine (43.05 g, 0.506 mol), triethylorthoformate (37.49 g, 0.254 mol), and glacial acetic acid (1.0 g, 17 mmol) in a 250 mL flask with a steam-jacketed condenser was heated to gentle reflux for 48 h. After cooling to rt, residual starting material was removed under reduced pressure. The crude material was then vacuum distilled (bp 105-115 °C, 0.1 mm Hg) to give TPM (17.1 g, 38.3%) which solidified upon standing: ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 1, CH), 2.62 (bs, 12, NCH_2), 1.49 (bs, 18, CH_2).

Nickel Boride.[63] The catalyst was prepared just before use. To a stirred solution of nickel(II) acetate tetrahydrate (2.49 g, 10 mmol) in water (100 mL) in a 250 mL beaker was added dropwise 20 mL of a 1.0 M solution of sodium borohydride in 0.1 M NaOH. After gas evolution had completely ceased, the aqueous solution was decanted. The black granular nickel boride was resuspended in distilled water, then again decanted. After several quick washings with water, the catalyst was washed twice with absolute ethanol and ready to use in the reduction.

12-Methoxyergoline (1). TPM **21** (2.4 g, 9 mmol) and **20** (800 mg, 3 mmol) in a 10 mL flask, were stirred at 110 °C overnight under an aspirator vacuum. The resulting dark red enamine **22** was transferred to a flame dried 100 mL two necked flask, and dissolved in absolute ethanol (50 mL). Freshly prepared nickel boride (570 mg, 4.5 mmol) was added to the solution, and the reaction was heated to reflux. To the mixture hydrazine

monohydrate (225 mg, 4.5 mmol) in ethanol (2 mL) was added dropwise, continuously heating at reflux for 4 h. After cooling to rt, the mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to give a dark brown solid, which was purified by centrifugal chromatography (0 → 10% methanol in CH_2Cl_2 under N_2/NH_3 atmosphere) to give a pale brown solid 1 (205 mg, 27.7%): mp 147-150 °C ; ^{1}H NMR ($CDCl_3$) δ 7.73 (bs, 1, NH), 7.11 (d, 1, ArH, J = 8.7 Hz), 6.89 (s, 1, ArH), 6.87 (d, 1, ArH, J = 8.9 Hz), 3.87 (s, 3, OCH_3), 3.50 (m, 1, ArCH), 3.32 (m, 2, $ArCH_2$), 3.02 (m, 2, NC*H*, NCH_2), 2.78 (dd, 1, NCH_2, J = 4.7 and 14.9 Hz), 2.03-1.73 (m, 4, CH_2), 1.72 (s, 1, NH); HR CIMS for $C_{15}H_{18}N_2O$ 243.1497 found 243.1501 (MH^+).

***N*-(6)-Methyl-12-methoxyergoline (2).** To 12-methoxyergoline (1) (53 mg, 0.22 mmol) in a 10 mL flask, a solution of fumaric acid (0.22 mmol) in methanol (2 mL) was added with stirring, then 37% formaldehyde (1.35 mmol, 110 μL) and $NaCNBH_3$ (56 mg, 0.85 mmol) were added. The mixture was stirred at rt overnight, and the volatile components were removed *in vacuo*. Water (10 mL) was added to the residue, which was basified with NH_4OH, and extracted with CH_2Cl_2 (3 x 10 mL). The organic extract was washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting dark brown residue was purified by column chromatography (silica, 10% EtOH in $CHCl_3$) to afford a pale brown solid (42 mg, 73.6%): mp 156-158 °C; ^{1}H NMR ($CDCl_3$, free base) δ 7.99 (bs, 1, NH), 7.09 (d, 1, ArH, J = 9.0 Hz), 6.86 (s, 1, ArH), 6.82 (d, 1, ArH, J = 9.3 Hz), 3.83 (s, 3, OCH_3), 3.55 (td, 1, ArCH, J = 3.9 and 12.6 Hz), 3.39 (m, 1, NCH), 2.98 (d, 2, $ArCH_2$, J = 9.3 Hz), 2.78 (dd, 2, NCH_2, J = 2.8 and 11.2 Hz), 2.63 (s,

3, NCH_3), 2.05-1.99 (m, 2, CH_2), 1.74 (m, 1, CH_2), 1.37 (m, 1, CH_2); HR CIMS for $C_{16}H_{20}N_2O$ 257.1654 found 257.1644 (MH^+).

***N*-(6)-Propyl-12-methoxyergoline (3).** A solution of 12-methoxyergoline (**1**) (100 mg, 0.413 mmol), K_2CO_3 (113 mg, 0.826 mmol), and iodopropane (0.515 mmol) in DMF (3 mL) was stirred at rt overnight. The residue after drying under high vacuum, was dissolved in CH_2Cl_2 (10 mL), filtered to remove the insoluble components, and the filtrate was concentrated *in vacuo*. The pale brown solid **3** (52 mg, 44.4%) was obtained after purification by chromatography (silica, 5% EtOH in $CHCl_3$); mp 178-181 °C (dec): ^{1}H NMR ($CDCl_3$, free base) δ 7.99 (bs, 1, NH), 7.11 (d, 1, ArH, J = 9.3 Hz), 6.90 (s, 1, ArH), 6.84 (d, 1, ArH, J = 9.3 Hz), 3.96 (s, 3, OCH_3), 3.72 (m, 1, ArCH), 3.38 (m, 2, $ArCH_2$), 3.05 (m, 1, NCH), 2.72 (m, 2, NCH_2), 2.23 (t, 2, $NCH_2CH_2CH_3$, J = 7.6 Hz), 2.06-1.34 (m, 6, $ArCHCH_2CH_2$, $NCH_2CH_2CH_3$), 0.99 (t, $NCH_2CH_2CH_3$, J = 7.3 Hz); HR CIMS for $C_{18}H_{24}N_2O$ 285.1987 found 285.1960 (MH^+).

6-Methoxyindole

Methyl 6-methoxy-indole-2-carboxylate (26).[69] To anhydrous methanol (650 mL) in a flame dried 2 L three neck flask equipped with mechanical stirrer, dropping funnel, and reflux condenser was added sodium (30 g, 1.3 mol) in small pieces with stirring. After the sodium was dissolved completely, the reflux condenser was exchanged to low temperature thermometer and the solution was cooled to -10 °C in an ice/salt bath. A mixture of methyl azidoacetate (**23**) (150 g, 1.3 mol) and *p*-methoxybenzaldehyde (**24**) (70 g, 0.514 mol) in anhydrous methanol (100 mL) was added dropwise *via* a dropping funnel to the

sodium methoxide solution over 2 h, maintaining the temperature below 0 °C, and stirred continuously for an additional hour at 0-5 °C. The reaction was poured over ice (200 g), and filtered. The pale yellow filter cake, azidocinnamate **25**, was washed on the filter with water, briefly air dried by suction, and then dissolved in xylene (1.5 L). The resulting solution was then added dropwise over 5 h into a 5 L flask containing xylene (1 L) at reflux. After addition the reaction was stirred for an additional hour at reflux, cooled, and concentrated to 800 mL *in vacuo*. The mixture was cooled in an ice/salt bath, which led to a crystalline precipitate. After filtration and washing the filter cake with hexane, indole-2-carboxylate **26** was obtained as off-white needles (72.6 g, 68.8%): mp 117-118 °C [Lit[69] 118-120 °C]; ^{1}H NMR ($CDCl_3$) δ 8.89 (bs, 1, NH), 7.65 (dd, 1, ArH, J = 2.4 and 9.0 Hz), 7.17 (d, 1, ArH, J = 2.4 Hz), 6.86 (s, 1, ArH), 6.84 (d, 1, ArH, J = 9.0 Hz), 3.94 (s,3, OCH_3), 3.87 (s, 3, $COOCH_3$).

6-Methoxyindole-2-carboxylic acid (27).[69] Indole-2-carboxylate (50 g, 0.24 mol) **26** was added to an aqueous solution of 2N NaOH (1.6 L). The resulting suspension was heated at 80-90 °C until homogeneous, after which the solution was heated at reflux for an additional hour. The solution was cooled to rt, and acidified with 3N HCl (1 L). The resulting white precipitate was filtered, washed on the filter with water, and dried under high vacuum over P_2O_5 to give **27** (42.3 g, 90.8%): mp 203-204 °C [Lit.[69] 204-206 °C]; ^{1}H NMR (DMSO-d_6) δ1 2.71 (bs, 1, COOH), 11.53 (s, 1, NH), 7.48 (d, 1, J = 8.7 Hz), 6.99 (s, 1, ArH), 6.84 (d, 1, ArH, J = 2.1 Hz), 6.71 (dd, 1, ArH, J = 2.0 and 8.8 Hz), 3.76 (s, 3, OCH_3).

6-Methoxyindole (28).[69] A mixture of indole-2-carboxylic acid **27** (40 g, 0.21 mol), and Cu powder (9 g) in anhydrous *N*-methylpyrrolidinone (1.2 L) was heated at 220-230 °C for 6 h under an Ar purge. The reaction was cooled, filtered through a pad of Celite, and diluted with water (1 L), and then extracted with ether (3 x 200 mL). The organic extract was washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting dark brown solid was purified by short column chromatography (silica, 7:3, hexane/EtOAc), and then Kugelrohr distillation to give a white crystalline solid (18.2 g, 64.8%): mp 87-89 °C [Lit.[69] 92-94 °C]; ^{1}H NMR δ 8.01 (bs, 1, NH), 7.50 (d, 1, ArH, J = 6.9 Hz), 7.09 (s, 1, ArH), 6.88 (s, 1, ArH), 6.79 (d, 1, ArH, J = 7.2 Hz), 6.47 (s, 1, ArH), 3.84 (s, 3, OCH_3).

6-Methoxyindole-3-acetic acid derivatives

6-Methoxyindole-3-acetic acid methyl ester (32).[70] To a precooled solution of 6-methoxyindole **28** (2g, 13.59 mmol) in THF (30 mL) at 10 °C in an ice/ethanol bath was added *n*-BuLi (9.3 mL, 14.9 mmol, 1.6 M in hexane) dropwise *via* a syringe, and the reaction mixture was stirred for 15 min. To the resulting yellow solution was added a solution of $ZnCl_2$ (14 mL, 1 M in Et_2O), and the mixture was then stirred for 2 h at rt, concentrated under reduced pressure to give a wax which was dissolved in anhydrous toluene (30 mL). To the solution methyl 2-bromoacetate (2.08 g, 13.6 mmol) was added. The mixture was stirred for 4 h at rt and then poured into 1N HCl (60 mL) and ethyl acetate (60 mL). The layers were separated, and the organic layer was washed with water

(2 x 60 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 7:3, hexane/EtOAc) to provide 6-methoxyindole-2-acetic acid methyl ester (**32**) as a white solid (1.20 g, 40.3%): mp 92-93 °C [Lit.[70] 92 °C]; ^{1}H NMR δ 8.04 (bs, 1, NH), 7.46 (d, 1, ArH, J = 8.7 Hz), 7.05 (s, 1, ArH), 6.84 (d, 1, ArH, J = 1.9 Hz), 6.79 (dd, 1, ArH, J = 2.0 and 8.7 Hz), 3.82 (s, 3, OCH_3), 3.73 (s, 2, $ArCH_2$), 3.68 (s, 3, $COOCH_3$). Unreacted starting material **28** (980 mg, 49%) was also recovered.

6-Methoxy-1-(*p*-toluenesulfonyl)indoline-3-acetic acid methylester (33). To a solution of indole **32** (800 mg, 3.6 mmol) in HOAc (15 mL) was added $NaCNBH_3$ (920 mg, 14.4 mmol) portionwise with stirring at 15 °C. The reaction was stirred at rt for 4 h, then extracted with CH_2Cl_2 (3 x 20 mL). The organic extract was washed with saturated $NaHCO_3$ (30 mL) and water (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The oily residue was taken up into CH_2Cl_2 (3 mL), and cooled to 0 °C. To the solution were added NEt_3 (760 mg, 7.6 mmol) and *p*-TsCl (3.6 mmol). The reaction mixture was stirred at rt until the TLC indicated the reaction was completed, then washed with 10 % H_2SO_4 (3 mL) and water (5 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting brown solid was purified by column chromatography (silica, 7:3, EtOAc/hexane) to give a white solid (1.06 g, 78.1%): mp 108-110 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, 2, ArH, J = 8.4 Hz), 7.23 (d, 3, ArH, J = 7.8 Hz), 6.92 (d, 1, ArH, J = 8.4 Hz), 6.51 (dd, 1, ArH, J = 2.1 and 8.4 Hz), 4.07 (dd, 1, NCH_2, J = 7.2 and 8.1 Hz), 3.81 (s, 3, OCH_3), 3.67 (s,3, $COOCH_3$), 3.64 (dd, 1, NCH_2, J = 5.8 and 8.4 Hz), 3.51-3.42 (m, 1,

ArH), 2.47 (dd,1, CH_2CO, J = 5.2 and 15 Hz), 2.43 (s, 3, $ArCH_3$), 2.18 (dd, 1, CH_2CO, J = 9.3 Hz and 15 Hz); CIMS 376 (MH^+); Anal ($C_{19}H_{21}NO_5S$) C, H, N.

6-Methoxy-1-(p-toluenesulfonyl)indoline-3-acetic acid (36). A solution of ester **33** (600 mg, 1.59 mmol) in methanol (30 mL) and 1N aqueous KOH (5 mL) was stirred at 55 °C for 2 h, and cooled to rt. The reaction was acidified to pH 2 with 10 % H_2SO_4 in an ice bath, and extracted with ethyl acetate (3 x 50 mL). The organic extract was washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a white solid **36** (553 mg, 95.8%): mp 168-170 °C; ^1H NMR (DMSO-d_6) δ 7.68 (d, 2, ArH, J = 8.1 Hz), 7.35 (d, 2, ArH, J = 8.1 Hz), 7.69 (d, 1, ArH, J = 8.4 Hz), 6.99 (d, 1, ArH, J = 2.1 Hz), 6.51 (dd, 1, ArH, J = 2.1 and 8.4 Hz), 3.98 (dd, 1, NCH_2, J = 7.2 and 8.5 Hz), 3.73 (s, 3, OCH_3), 3.55 (dd, 1, NCH_2, J = 5.8 and 8.4 Hz), 3.08-2.97 (m, 1, ArH), 2.32 (s, 3, $ArCH_3$), 2.47 (dd,1, CH_2CO, J = 5.2 and 15 Hz), 1.68 (m, 1, $ArCHCH_2$), 1.28 (m, 1, $ArCHCH_2$); CIMS 362 (MH^+).

<u>6-Methoxyidole-3-propionic acid derivatives</u>

5-(6-Methoxyindolyl-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (41). A solution of 6-methoxyindole (**28**) (30 g, 0.203 mol), Meldrum's acid **40** (29.4 g, 0.203 mol) and a 37% formaldehyde (16.8 mL, 0.203 mol) with proline (1.2 g) as a catalyst in CH_3CN (120 mL), was stirred at rt overnight. All volatile components were removed under reduced pressure to give a brown foam. The product was recrystallized from acetone/water to yield an off-white solid (50.4 g, 81.6%): mp 142-143 °C; ^1H NMR

(DMSO-d_6) δ 10.62 (bs, 1, NH), 7.43 (d, 2, ArH, J = 8.7 Hz), 6.84 (d, 2, ArH, J = 1.8 Hz), 6.79 (s, 1, ArH), 6.62 (dd, 1, ArH, J = 2.1 and 8.7 Hz), 4.69 (t, 1, COCHCO, J = 4.5 Hz), 3.72 (s, 3, OCH_3), 3.35 (d, 2, $ArCH_2$, J = 4.5 Hz), 1.74 (s, 6, $C(CH_3)_2$); Anal ($C_{16}H_{17}NO_5$) C, H, N.

6-Methoxyindole-3-propionic acid ethyl ester (42). To a solution of **41** (55 g, 0.181 mol) in pyridine (1.62 L) and absolute ethanol (180 mL) was added copper powder (1.2 g). The reaction was heated at reflux for 5 h, and cooled to rt. After filtering through a pad of Celite, the solvents were removed under reduced pressure. The residual oil was taken up in ether (100 mL) and washed with 1 N HCl (50 mL), 20% NH_4Cl (50 mL) and water (50 mL), was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting brown oil was purified by Kugelrohr distillation (bp 130-135 °C, 0.05 mm Hg) to give an off white solid (34.6 g, 77.4%): mp 69-71 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (bs, 1, NH), 7.53 (d, 1, ArH, J = 8.6 Hz), 7.33 (s, 1, ArH), 6.87 (m, 2, ArH), 4.25 (2, q, OCH_2, J = 4.4 Hz), 3.90 (s, 3, OCH_3), 3.12 (t, 2, $ArCH_2$, J = 7.5 Hz), 2.75 (t, 1, $COCH_2$, J = 7.5 Hz), 1.28 (t, 1, CH_2CH_3, J = 6.6 Hz); CIMS 248 (MH^+).

6-Methoxy-1-(*p*-toluenesulfonyl)indoline-3-propionic acid ethyl ester (43). This compound **43** was prepared from **42**(20 g, 80.9 mmol) following the procedure used for the preparation of 6-methoxy-1-(*p*-toluenesulfonyl)indoline-3-acetic acid methyl ester (**33**). Purification by column chromatography (silica, 4:1, hexane/EtOAc) gave **43** as a white solid (26.65 g, 82.3%): mp 130-132 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, 2, ArH,

J = 8.4 Hz), 7.23 (d, 3, ArH, J = 7.8 Hz), 6.92 (d, 1, ArH, J = 8.4 Hz), 6.51 (dd, 1, ArH, J = 2.1 and 8.4 Hz), 4.06 (2, q, OCH_2, J = 6.9 Hz), 3.94 (dd, 1, NCH_2, J = 7.2 and 9.0 Hz), 3.81 (s, 3, OCH_3), 3.56 (dd, 1, NCH_2, J = 8.4 and 9.0 Hz), 3.20 (m, 1, ArH), 2.36 (s, 3, $ArCH_3$), 2.18 (t, 1, CH_2CO, J = 6.5 Hz), 1.88 (m, 1, $ArCHCH_2$), 1.56 (m, 1, $ArCHCH_2$); CIMS 402 (MH^+).

6-Methoxy-1-(*p*-toluenesulfonyl)indoline-3-propionic acid (44). This compound was prepared in 84.0% yield from **43** (25 g, 62.3 mmol) using the method described for the preparation of 6-methoxy-1-(*p*-toluenesulfonyl)indoline-3-acetic acid **36**: mp 144-147 °C; ^{1}H NMR (DMSO-d_6) δ 12.16 (bs, 1, COOH), 7.76 (d, 2, ArH, J = 8.4 Hz), 7.44 (d, 2, ArH, J = 8.1 Hz), 7.12 (d, 1, ArH, J = 8.4 Hz), 7.07 (d, 1, ArH, J = 2.3 Hz), 6.63 (dd, 1, ArH, J = 2.2 and 8.4 Hz), 4.05 (dd, 1, NCH_2, J = 8.7 and 9.0 Hz), 3.81 (s, 3, OCH_3), 3.56 (dd, 1, NCH_2, J = 8.4 and 9.0 Hz), 3.15 (m, 1, ArH), 2.40 (s, 3, $ArCH_3$), 2.18 (t,1, CH_2CO, J = 7.8 Hz), 1.74 (m, 1, $ArCHCH_2$), 1.36 (m, 1, $ArCHCH_2$); CIMS 374 (MH^+).

6-Methoxy-1-(p-toluenesulfonyl)indoline-3-propionaldehyde (47). The ester **43** (700 mg, 1.74 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to -78 °C. To the solution was added 1.74 mL of DIBAL (1 M in CH_2Cl_2) dropwise and the reaction was stirred for 10 min at -78 °C. After monitoring the reaction by TLC analysis, 0.87 mL of additional DIBAL (1 M in CH_2Cl_2) was added, and the reaction was stirred for an additional 5 min, which led to the completion of the reaction. A solution of 0.1 M tartaric acid (20 mL) was added to the reaction and the solution was stirred at rt for an hour, and

basification with 1N NaOH. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with water (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an off-white solid, This product was purified by column chromatography (silica, 7:3, hexane/EtOAc), and then crystallized from Et_2O/hexane to give white needles (465 mg, 74.6%): mp 99-101 °C; ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1, CHO), 7.68 (d, 2, ArH, J = 8.4 Hz), 7.23 (d, 3, ArH, J = 8.1 Hz), 6.92 (d, 1, ArH, J = 8.1 Hz), 6.51 (dd, 1, ArH, J = 2.1 and 8.1 Hz), 3.93 (dd, 1, NCH_2, J = 7.2 and 9.0 Hz), 3.81 (s, 3, OCH_3), 3.55 (dd, 1, NCH_2, J = 8.4 and 9.0 Hz), 3.12 (m, 1, ArH), 2.36 (s, 3, $ArCH_3$), 2.30 (t, 1, CH_2CO, J = 7.2 Hz), 1.78 (m, 1, ArCHCH_2), 1.56 (m, 1, ArCHCH_2); Anal ($C_{19}H_{21}NO_4S$) C, H, N .

6-Methoxyindole-3-propionic acid (48).[123] A solution of ester **42** (494 mg, 2 mmol) in a solution of aqueous 5N KOH (1 mL) and ethanol (6 mL) was heated at reflux for one hour. After cooling, the solution was acidified with aqueous 3N HCl. The resulting precipitate was filtered, washed on the filter with water, and dried under high vacuum to yield a white solid (402 mg, 91.8%): mp 158-161 °C [Lit.[123] 165 °C]; ^{1}H NMR ($CDCl_3$) δ 10.56 (bs, 1, NH), 7.37 (d, 2, ArH, J = 8.6 Hz), 6.96 (s, 1, ArH), 6.83 (s, 1, ArH), 6.63 (d, 1, ArH, J = 8.7 Hz), 3.75 (s, 3, OCH_3), 2.87 (t, 2, $ArCH_2$, J = 7.5 Hz), 2.55 (t, 2, CH_2CO, J = 7.3 Hz); CIMS 220 (MH^+).

6-Methoxy-(1-trimethylacetyl)indol-3-propionic acid (49). To a -78 °C solution of **48** (300 mg, 1.37 mmol) in THF (15 mL) was added *n*-BuLi (1.8 mL, 1.6 M in hexane) under

an Ar atmosphere, and the reaction was stirred for 10 min. Trimethylacetyl chloride (185 μL, 1.5 mmol) was added to the mixture, which was then stirred for 15 min at -78 °C, 15 min at -50 °C and 15 min at -20 °C. The reaction was quenched with saturated NH_4Cl (20 mL), and extracted with ethyl acetate (3 x 15 mL). The organic extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. This compound was purified by crystallization from ether to give a white solid (304 mg, 73.2%): mp 180-182 °C; ^1H NMR δ ($CDCl_3$) 8.17 (d, 1, ArH, J = 2.1 Hz), 7.48 (s, 1, ArH), 7.39 (d, 1, ArH, J = 8.5 Hz), 6.94 (dd, 1, ArH, J = 2.2 and 8.5 Hz), 3.90 (s, 3, OCH_3), 3.05 (t, 2, $ArCH_2$, J = 7.4 Hz), 2.79 (t, 2, $COCH_2$, J = 7.4 Hz), 1.51 (s, 9, $C(CH_3)_3$); CIMS 304 (MH^+)

6-Methoxyindole-tricarbonylchromium complexes.

η^6-(6-Methoxyindole)tricarbonylchromium(0) (50). To a 250 mL three necked flask equipped with a simple air condenser (not a spiral type from which subliming $Cr(CO)_6$ is washed back less efficiently) and gas inlet were placed 6-methoxyindole (**28**) (2 g, 13.59 mmol), chromium hexacarbonyl (3 g, 13.27 mmol), dibutylether (70 mL) and THF (7 mL). A bubbler was placed at the top of the condenser to exclude air. The mixture was degassed and blanketed with Ar, and was then heated at 150 °C overnight with stirring under an Ar atmosphere, during which the color changed from white to orange. The reaction mixture was cooled to rt, filtered through a pad of Celite, which was then washed on the filter with THF. The filtrate, containing solvent and $Cr(CO)_6$ was concentrated under reduced pressure to give a yellow crystalline solid. After column

chromatography (silica, 7:3, hexane/EtOAc), the chromium complex **50** was obtained as a yellow crystalline solid (1.53 g, 40.3%), along with recovered starting material **28** (1.1 g, 55%). An analytical sample was prepared by crystallization from ether/pentane; mp 132-134 °C (dec); ^{1}H NMR δ ($CDCl_3$) 7.67 (bs, 1, NH), 7.14 (dd, 1, ArH, J = 2.1 Hz), 6.39 (d, 1, ArH, J = 7.0 Hz), 6.29 (s, 1,ArH), 5.91 (s, 1, ArH), 5.01 (1, dd, ArH, J = 1.8 Hz, 7.0 Hz) 3.75 (s, 3, OCH_3); Anal. ($C_{12}H_9CrNO_4Si$) C, H, N.

η^6-(6-Methoxy-1-triisopropylsilylindole)tricarbonylchromium(0) (51). The compound **50** (1.3 g, 4.5 mmol) was dissolved in dry THF (33 mL) and cooled to 0 °C in an ice bath. To the solution NaH (250 mg, 5.85 mmol, 60% in mineral oil) was added, and the mixture was stirred for 20 min at 0 °C. Chlorotriisopropylsilane (1.4 mL, 5.85 mmol) was added and the reaction mixture was stirred for 30 min at 0 °C. All volatile components were removed under reduced pressure and the residual oil was taken up with ether (40 mL), washed with water (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The compound **51** was purified by column chromatography (silica; 9:1, hexane/EtOAc), and crystallized from ether/pentane to give yellow prisms (1.7 g, 85.0%): mp 126-127 °C; ^{1}H NMR δ ($CDCl_3$) 7.16 (d, 1, ArH, J = 6.6 Hz), 6.35 (s, 1, ArH), 6.32 (d, 1, ArH, J = 2.1 Hz), 6.07 (s, 1, ArH), 4.89 (1, dd, ArH, J = 2.2 Hz, 6.9 Hz) 3.72 (s, 3, OCH_3), 1.61 (m, 3, SiCH), 1.22 (d, 9, $CHCH_3$, J = 7.5 Hz), 1.13 (dd, 9, $CHCH_3$, J = 7.5 Hz); Anal ($C_{21}H_{29}CrNO_4Si$) C, H, N.

6-Methoxyindole-4-acetonitrile (52). To a -78 °C precooled solution of acetonitrile (35 μL) in dry THF (3.5 mL) was added n-BuLi (320 μL, 1.6 M in hexane), and the reaction mixture was stirred for 30 min at -78 °C. A solution of **51** (200 mg, 0.44 mol) in THF (3.5 mL) was added dropwise to the reaction, and stirred for 2.5 h at -78 °C, which was quenched with a cold solution of iodine (600 mg) in THF (3.5 mL), then stirred for 1 h at -78 °C, and for 3 h at rt. Tetrabutylammonium fluoride (880 μL, 1M in THF) was added to the solution, and the mixture was stirred for 10 min at rt. The reaction mixture was poured into a saturated solution of Na_2SO_3 (15 mL) and the layers were separated. The aqueous layer was extracted with ether (10 mL x 3), and the combined organic extract was washed with a saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. After purification by column chromatography (silica, 7:3, hexane/EtOAc), the compound **52** was obtained as a white solid (45 mg, 54.9%): ^{1}H NMR δ ($CDCl_3$) 8.18 (bs, 1, ArH, NH), 7.30 (d, 1, ArH, J = 9.0 Hz), 7.15 (d, 1, ArH, J = 2.4 Hz), 6.86 (1, d, ArH, J = 2.2 Hz), 6.84 (d, 1, ArH, J = 1.3 Hz), 3.83 (s, 5, OCH_3, $ArCH_2$).

1,3-Dihydroisothianaphthene (57).[92] To a solution of Na_2S (780 mg, 10 mmol) in ethanol (10 mL) was added finely powdered α,α'-dibromo-*o*-xylene (2.63 g, 10 mmol) portiowise over 1 h with stirring. The hot reaction mixture was allowed to cool to rt, and water (5 mL) was added to the reaction. The solution was filtered to remove amorphous gray precipitate, and the filtrate was extracted with pentane (3 x 15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil, which solidified below 20 °C. The crude mixture was purified by vacuum distillation (bp 47-52 °C, 0.4 mm Hg)

to give **57** (820 mg, 60.3%): ^{1}H NMR δ ($CDCl_3$) 7.32-7.14 (m, 4, ArH), 4.19 (4, s, $ArCH_2$).

η^6-(6-Methoxyindole-5-acetate)tricarbonylchromium(0) (60). A solution of **51** (300 mg, 0.67 mmol) in dry THF (35 mL) was cooled to -78 °C. To the solution was added TMEDA (670 μL) followed by n-BuLi (820 μL, 1.6 M in hexane). The mixture was allowed to warm to rt, and was then stirred overnight. The reaction was quenched with a cold solution of 5% (10 mL) NH_4Cl, and the layers were separated. The aqueous layer was extracted with ether (3 x 5 mL), and the combined organic extract was washed with water (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica 7:3, hexane/EtOAc) to afford **60** as a yellow solid (42 mg, 17.4 %): ^{1}H NMR ($CDCl_3$) δ 8.06 (bs, 1, NH), 7.66 (s, 1, ArH), 7.08 (s, 1, ArH), 6.48 (s, 1, ArH), 4.00 (d, 1, $ArCH_2$, 9.7 Hz), 3.81 (s, 3, OCH_3), 3.66 (d, 1, $ArCH_2$, 9.7 Hz), 3.44 (s, 3, $COOCH_3$).

6-Methoxyindole-4-boronic acid

2-Bromo-4-methoxybenzaldehyde (62).[96, 97] To a precooled solution of 3-bromoanisole (25 g, 0.13 mol) in CH_2Cl_2 (100 mL) at 0 °C, $TiCl_4$ (40.5 g, 0.21 mol) was added and the reaction was mechanically stirred at 0 °C for 30 min. To the mixture was added α,α'-dichloromethylmethylether dropwise over 30 min *via* a dropping funnel, and the solution was stirred at 0 °C for 30 min, and then at rt for 2 h. The reaction mixture was poured over ice (100 g), and stirred for 30 min, and then the layers were separated. The

aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), which was combined with the organic layer. The organic extract was washed with water (100 mL), saturated $NaHCO_3$ (100 mL), then water (100 mL), was dried (Na_2SO_4), filtered and concentrated *in vacuo*. This crude mixture of aldehydes, which showed a 2:1 ratio of 2-bromo-4-methoxybenzaldehyde (**62**) and 4-bromo-2-methoxybenzaldehyde (**63**) based on the ^1H NMR spectra, was dissolved in CH_2Cl_2 (1000 mL) in a 2 L three necked flask equipped with mechanical stirrer. To the stirred solution was added anhydrous $AlCl_3$ (100 g, 0.75 mol) portionwise,with stirring at rt for 6 h. The demethylated compound, 4-bromo-2-hydroxybenzaldehyde (**64**) showed a higher R_f value on TLC (silica, 9:1, hexane/EtOAc) than that of aldehyde **63**. The reaction mixture was cautiously added with stirring to ice (500 g) in a 4 L beaker, and the mixture was stirred for one hour. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extract was washed with water, and then with 0.5 N NaOH (3 x 200 mL) to extract phenol **64**. The organic layer was washed with water (200 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting brown solid was purified by kugelrhor distillation (bp 55-65 °C in 0.1 mm Hg) to give a white crystalline solid (13.5 g, 48%): ^1H NMR 10.66 (s, 1, C*H*O) δ, 7.88 (d, 1, ArH, $J = 8.7$ Hz), 7.12 (d, 1, ArH, $J = 2.1$ Hz), 6.92 (dd, 1, ArH, $J = 2.1$ and 8.7 Hz).

Methyl 4-bromo-6-methoxy-indole-2-carboxylate (65). This compound was prepared by the same procedure used for the synthesis of compound **26**, except that benzaldehyde **62** (12 g, 58.5 mmol) and methyl azidoacetate (27 g, 230 mmol) were dissolved in dry

THF (20 mL) rather than methanol before addition to a solution of sodium methoxide (230 mmol in methanol). The carboxylate **65** was obtained as a white solid (8.1 g 49.1%). An analytical sample was crystallized from toluene to provide white crystals: mp 206-207 °C; ^{1}H NMR ($CDCl_3$) δ 8.89 (bs, 1, NH), 7.17 (d, 1, ArH, J = 1.9 Hz), 7.02 (d, 1, ArH, J = 1.9 Hz), 6.76 (s, 1, ArH) 3.92 (s, 3, OCH_3), 3.82 (s, $COOCH_3$); Anal. ($C_{11}H_{10}O_3NBr$) C, H, N.

4-bromo-6-methoxy-indole-2-carboxylic acid (66). This compound was prepared in 92% yield from **65** (8 g, 28.1 mmol) by the same procedure used for the synthesis of compound **27** : mp 256-248 °C (dec); ^{1}H NMR (DMSO-d_6) δ 12.96 (1, bs, COOH), 11.92 (bs, 1, NH), 6.98 (d, 1, J = 1.7 Hz), 6.87 (d, 1, ArH, J = 1.7 Hz), 6.86 (s, 1, ArH), 3.77 (s, 3, OCH_3).

4-bromo-6-methoxy-indole (67). This compound was obtained in 60.7% yield from **66** (7.0 g, 25.9 mmol) by the same procedure used for the synthesis of compound **28.** An analytical sample was crystallized from Et_2O/hexane as off white amorphous crystals: mp 53-54 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (bs, 1, NH), 7.17 (dd, 1, ArH, J = 1.9 and 2.7 Hz), 6.99 (d, 1, ArH, J = 1.9 Hz), 6.82 (d, 1, ArH, J = 1.5 Hz), 6.49 (d, 1, ArH, J = 2.1 Hz), 3.83 (s, 3, OCH_3); Anal. ($C_{11}H_{10}O_3NBr$) C, H, N.

6-Methoxyindole-4-boronic acid (68). In a flame-dried 100 mL three necked flask a suspension of KH (1.0 g, 8.8 mmol, 35 % suspension in mineral oil) in THF (20 mL) was

cooled to 0 °C. To the suspension was added a solution of indole **67** (2 g, 8.8 mmol) in THF (20 mL) dropwise, followed by stirring for 15 min at 0 °C. The resulting pink solution was cooled to -78 °C, and a precooled solution of *t*-BuLi (10 mL, 1.7 M in pentane) at -78 °C was added *via* a cannula, then the mixture was stirred for 10 min. To the yellow suspension at -78 °C was added triisopropyl borate (17.6 mmol), and the reaction mixture was stirred for 6 h while allowing the temperature to warm to rt. The reaction mixture was poured into an ice-cooled 1 M solution of H_3PO_4 (100 mL), and stirred for 1 h. The layers were separated, and the aqueous layer was extracted with ether (2 x 10 mL). The boronic acid **68** was extracted into 1 N NaOH (3 x 20 mL), and was then liberated by acidification with 1N HCl, extracted into ether (3 x 20 mL). The organic extract was washed with water (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown solid (1.24 g, 73.8%), which was used in the next step without further purification.

Isoquinoline-3-carboxylate-4-*O*-triflate

Methyl 2-formylbenzoate (69).[100] To a mechanical stirred suspension of 2-formylbenzoic acid (50 g, 0.33 mol) and K_2CO_3 (140 g, 1 mol) in acetone (1.5 L) was added CH_3I (50 g, 0.35 mol) dropwise followed by heating at reflux for 1.5 h. Additional CH_3I (50g, 0.35 mol) was added dropwise to the reaction at reflux, followed by additional stirring for 1.5 h at reflux. The mixture was cooled to rt, and filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in ether (300 mL),

washed with 2N NaOH (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a white solid (46 g, 84.1%).

***B,B*-Diethylboroxazolidone (71).**[101] A mixture of gycine (75 g, 0.67 mol), which was finely ground and dried under high vacuum, and triethylborane (0.80 mol, 1 M in THF) in THF (500 mL) was stirred at rt for 60 h. The suspension was filtered, and the filtrate was concentrated under reduced pressure to give an off-white solid (61 g, 63.6%), which was used for the next step without further purification: mp 181-184 °C (Lit.[101] mp 174 °C); ^{1}H NMR (DMSO-d_6) δ 6.05 (bs, 1, NH), 3.39 (d, 2, NHCH_2CO), 0.65 (t, 6, CH_2CH_3, J = 7.8 Hz), 0.19 (q, 4, BCH_2, J = 7.8 Hz).

***N*-[*o*-(Methoxycarbonyl)benzylidene]-*B,B*-diethylboroxazolidone (72).**[100] The benzaldehyde **69** (32.8 g, 0.2 mol) and boroxazolidine **71** (28.6 g, 0.2 mol) were dissolved in benzene (500 mL) with warming and the solution was heated to reflux with a Dean-Stark trap for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was treated with ether. The resulting precipitate was collected by filtration, and dried under high vacuum to yield an off-white solid (51 g, 88.2%): mp 109-110 °C (Lit.[100] mp 108-110 °C); ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1, ArCHN), 8.23 (d, 1, ArH, J = 7.6 Hz), 7.79-7.68 (m, 2, ArH), 7.37 (d, 1, ArH, J = 7.5 Hz) 4.10 (d, 2, NCH_2CO, J = 2.8 Hz), 3.95 (s, 3, OCH_3), 0.84 (t, 6, CH_2CH_3), 0.72-0.51 (m, 4, BCH_2).

***B,B*-Diethylboryl-4-Hydroxyisoquinoline-3-carboxylate (73).**[100] A solution of borate **72** (29 g, 0.1 mol) in DMF (800 mL) was cooled to -40 °C, and *t*-BuOK (11.2 g, 0.1 mol) was added portionwise through a solids addition funnel. The cooling bath was removed, the reaction mixture was stirred at rt for 3 h, and then poured into a cold solution of 20% aqueous citric acid (1.2 L). The resulting precipitate was filtered and dissolved in $CHCl_3$, washed with water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a pale yellow solid (21 g, 81.7%): mp 144-147 °C (Lit.[100] mp 150-151 °C); ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1, ArH), 8.54 (d, 1, ArH, J = 7.5 Hz), 8.17 (d, 1, ArH, J = 8.2 Hz), 8.04-7.92 (m, 2, ArH), 0.85-0.52 (m, 10, BCH_2CH_3).

4-Hydroxyisoquinoline-2-carboxylic acid (74).[100] Isoquinoline **73** (20 g, 77.8 mmol) was dissolved in ethanol (400 mL) with gentle heating, and 8-hydroxyquinoline (12.4 g, 85 mmol) was added. The solution was heated at 70 °C for 2 h. After cooling, the precipitate was collected by filteration, and washed on the filter with ether to give a white crystalline solid (8 g). The filtrate was concentrated to 200 mL, and an additional 1.2 g of **73** was obtained (overall 9.2 g, 62.6%): mp 224-226 °C (Lit.[100] mp 219-220 °C); ^{1}H NMR (DMSO-d_6) δ 8.80 (s, 1, ArH), 8.41-8.35 (m, 2, ArH), 8.04-7.92 (m, 2, ArH).

Methyl 4-hydroxyisoquinoline-3-carboxylate (75). A solution of $(CH_3)_3SiCHN_2$ (50 mL, 2 M in hexane) was added dropwise to a stirred solution of carboxylic acid **74** (8.5 g, 45 mmol) in benzene (350 mL) and methanol (100 mL) at rt; the addition was accompanied by vigorous gas evolution. The reaction mixture was stirred at rt for 1 h,

and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was extracted with ethyl acetate, and the solvent was removed *in vacuo* to give a white solid. The compound was crystallized from EtOAc/hexane to give white fluffy needles (5.4 g, 59.3%): mp 128-129 °C; ^{1}H NMR ($CDCl_3$) δ 11.74 (s, 1, OH), 8.80 (s, 1, ArH), 8.46 (d, 1, ArH, J = 7.5 Hz), 7.94 (d, 1, ArH, J = 7.5 Hz), 7.78 (m, 2, ArH), 4.09 (s, 3, $COOCH_3$). Anal. ($C_{11}H_9O_3N$) C, H, N.

Methyl 4-[[(trifluoromethyl)sulfonyl]oxy]isoquinoline-3-carboxylate. (76). Compound **75** (3.27 g, 16.2 mol) was dissolved in anhydrous CH_2Cl_2 (90 mL) and pyridine (5.2 mL), and the solution was cooled to -30 °C. To the solution trifluoromethanesulfonic anhydride (5 g, 17.7 mmol) was added dropwise. The reaction mixture was allowed to warm to 0 °C, and was stirred at 0 °C for 6 h. The reaction mixture was diluted with ether (500 mL), and stirred for 10 min, then filtered. The filtrate was washed with 1N HCl (100 mL) and 2 M Na_2CO_3 (100 mL), dried (Na_2SO_4), and was filtered, and concentrated under reduced pressure to give a white solid, which was crystallized from CH_2Cl_2/hexane as white needles (3.6 g, 66.4%): mp 80-81 °C; ^{1}H NMR ($CDCl_3$) δ 9.62 (s, 1, ArH), 8.21 (d, 1, ArH, J = 8.4 Hz), 8.14 (d, 1, ArH, J = 8.1 Hz), 7.97-7.59 (m, 2, ArH), 4.07 (s,3, $COOCH_3$). Anal. ($C_{11}H_9O_3N$) C, H, N.

<u>Indoloisoquinoline-3-carboxylate derivatives</u>

Methyl 4-(6-methoxy4-indolo)-isoquinoline-3-carboxylate (77). A mixture of boronic acid **68** (420 mg, 2.2 mmol), *O*-triflate **76** (670 mg, 2 mmol), finely powdered K_3PO_4

(640 mg, 3 mmol), BHT (308 mg, 1.4 mmol) and $PdCl_2$(dppf) (80 mg, 0.1 mmol) in anhydrous dioxane (10 mL) was degassed and blanketed with Ar, and then heated at reflux for 2.5 h. The reaction mixture was cooled and filtered through a pad of Celite, and washed with ether (15 mL). Water (10 mL) was added to the filtrate, and the layers were separated. The aqueous layer was extracted with ether (2 x 5 mL), the organic extract was washed with 1N NaOH (10 mL) to remove the excess boronic acid, then brine (10 mL), and water (10 mL), dried (Na_2SO_4), was filtered and concentrated under reduced pressure. After purification by column chromatography (silica, 1:1, hexane/EtOAc), **77** was obtained as a pale yellow solid (480 mg, 72.4%): mp 167-168 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1, ArH), 8.18 (bs, 1, NH), 8.06 (d, 1, ArH, J = 8.1 Hz), 7.69-7.55 (m, 3, ArH), 7.01 (m, 1, ArH), 6.97 (d, 1, ArH, J = 1.8 Hz) 6.75 (d, 1, ArH, J = 2.0 Hz), 3.86 (s,3, OCH_3), 3.67 (s, 3, $COOCH_3$); CIMS 333 (MH^+).

***Cis*-Methyl 4-(6-methoxy-4-indolo)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (83).** A solution of 10% methanolic HCl was added dropwise to a mixture of **77** (86 mg, 0.26 mmol), $NaCNBH_3$ (65 mg, 1 mmol) with a few drops of bromocresol (1 M in methanol) in methanol (3 mL) and THF (8.5 mL) with stirring, until the color of bromocresol remained yellow. The mixture was stirred at rt until TLC (silica, 4% MeOH in CH_2Cl_2) indicated the reaction was complete. The reaction mixture was poured into water (15 mL), basified with saturated Na_2CO_3, and extracted with $CHCl_3$ (3 x 15 mL). The organic extract was washed with water, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. After column chromatography, compound **83** was obtained as a

white foam (75 mg, 86.2%), confirmed as the *cis* isomer by comparison with the compound obtained by catalytic reduction of **77** (H_2/PtO_2): mp 84-86 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (bs, 1, NH), 7.27-7.13 (m, 4, ArH), 6.75 (s, 1, ArH), 6.42 (d, 1, ArH, J = 2.7 Hz) 6.15 (d, 1, ArH, J = 2.0 Hz), 5.02 (d, 1, Ar_2CH, J = 4.1 Hz), 4.55 (d, 2, $ArCH_2$, J = 10.2 Hz), 4.32 (d, 1, NCH, J = 4.3 Hz), 3.72 (s, 3, OCH_3), 3.41 (s, 3, $COOCH_3$); CIMS 337 (MH^+).

***Cis*-Methyl *N*-(2)-benzyl-4-(6-methoxy-4-indolo)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (84).** A mixture of the HCl salt of **83** (110 mg, 0.3 mmol), $NaCNBH_3$ (74 mg, 1.17 mmol) and benzaldehyde (200 μL, 1.97 mmol) in methanol (10 mL) was stirred at rt for 24 h. After all volatile components were removed under reduced pressure, the residue was treated with water (10 mL), and basified with NH_4OH. The basified solution was extracted with CH_2Cl_2 (3 x 5 mL) and the organic extract was washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. After column chromatography (silica, 7:3, hexane/EtOAc), **84** was obtained as an off-white solid (72 mg, 54.8%): ^{1}H NMR ($CDCl_3$) δ 8.27 (bs, 1, NH), 7.40-7.24 (m, 6, ArH), 7.10-6.99 (m, 4, ArH), 6.99 (s, 1, ArH), 6.56 (s, 1, ArH), 6.26 (s, 1, ArH), 5.08 (d, 1, Ar_2CH, J = 6.3 Hz), 4.28 (d, 1, $ArCH_2N$, J = 15.3 Hz), 4.04 (d, 1, NCH, J = 6.4 Hz), 3.88 (d, 1, $ArCH_2N$, J = 15.4 Hz), 3.72 (s, 3, OCH_3), 3.69 (s, 2, CH_2-Bn), 3.67 (s, 3, $COOCH_3$).

***Trans*-Methyl *N*-(2)-benzyl-4-(6-methoxy-4-indolo)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (85).** Sodium (140 mg, 6.0 mmol) was dissolved in dry methanol (12 mL),

and compound **84** (50 mg, 0.117 mmol) was added to the sodium methoxide solution. The reaction mixture was heated at reflux for 10 h, cooled and quenched with water (10 mL). All volatile components were removed under reduced pressure, and the residue was extracted with CH_2Cl_2 (3 x 5 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. After column chromatography (silica, 7:3, hexane/EtOAc), **85** was obtained as an off white solid (45 mg, 90.0%): ^{1}H NMR ($CDCl_3$) δ 8.05 (bs, 1, NH), 7.35 (d, 1, ArH, J = 4.3 Hz), 7.19-7.02 (m, 7, ArH), 7.01-6.96 (m, 2, ArH), 6.72 (d, 1, ArH, J = 1.6 Hz), 6.50 (s, 1, ArH), 6.30 (d, 1, ArH, J = 2.0 Hz), 4.98 (d, 1, Ar_2CH, J = 2.1 Hz), 4.16 (d, 1, $ArCH_2$, J = 15.6 Hz), 3.98 (d, 2, NCH, $ArCH_2$, J = 2.5 Hz), 3.93 (d, 1, CH_2-Bn, J = 4.5 Hz), 3.86 (d, 1, CH_2-Bn, J = 4.6 Hz), 3.75 (s, 3, OCH_3), 3.67 (s, 3, $COOCH_3$).

6-Methoxy-4-(4-isoquinolyl)-indole derivatives

6-Methoxy-4-(4-isoquinolyl)indole (88). The catalyst $Pd[(Ph)_3P]_4$ (50 mg) was added to a mixture of boronic acid **68** (230 mg, 1.2 mmol), 4-bromoisoquinoline (208 mg, 1 mmol) in DME (1.5 mL), and 2 M Na_2CO_3 (1.5 mL), and the reaction mixture was heated at reflux for 3 h. The mixture was cooled, diluted with 1N NaOH (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The organic extract was washed with brine (10 mL) and water (10 mL), dried (Na_2SO_4), and was filtered, and concentrated under reduced pressure. After column chromatography (silica, 1:1, hexane/EtOAc), the product was obtained as a pale yellow foam (325 mg, 79.5%): mp 136-138 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 9.27 (d, 1, ArH, J = 9.3 Hz), 8.61 (s, 1, ArH), 8.17 (bs, 1, NH), 8.04 (m, 1, ArH), 7.82 (m, 1, ArH), 7.61-7.55 (m, 2, ArH), 7.07 (dd, 1, ArH, J = 2.4 and 2.9 Hz), 7.01 (d, 1,

ArH, J = 1.7 Hz) 6.90 (d, 1, ArH, J = 2.2 Hz), 6.11 (d, 1, ArH, J = 2.1 Hz), 3.90 (s, 3, OCH_3); CIMS 275 (MH^+).

6-Methoxy-4-(4-isoquinolyl)indol-3-ylglyoxylic acid (90). A solution of oxalyl chloride (40 μL, 0.45 mmol) in dry ether (1 mL) was added dropwise to a solution of indole **88** (100 mg, 0.366 mmol) in dry ether (5 mL) at 0 °C, and the reaction mixture was stirred at rt for 8 h. The resulting yellow precipitate, indol-3-yl-glyoxyloyl chloride **89** was filtered off. The crude acid chloride was carefully added to wet THF, and the suspension was stirred overnight. The resulting solid was collected by filration and dried to yield the HCl salt of **90**, containing about 20 % of unreacted starting material **88**. The mixture of HCl salts was treated with 2 mL of 4% aqueous $Ba(OH)_2$ and dioxane (2 mL), and the solution was saturated with CO_2, and the $BaCO_3$ was filtered off. The filtrate was concentrated under reduced pressure. After extraction of starting material **88** with ether, **90** was obtained as a yellow solid (65 mg, 51.6%): ^{1}H NMR (DMSO-d_6) δ 12.43 (bs, 1, NH), 9.27 (d, 1, ArH, J = 8.7 Hz), 8.47 (s, 1, ArH), 8.38 (1, m, ArH), 8.25 (s, 1, ArH), 7.79 (m, 2, ArH), 7.44 (m, 1, ArH), 7.22 (s, 1, ArH), 6.89 (s, 1, ArH), 3.85 (s, 3, OCH_3).

<u>6-Methoxy-4-(3-pyridyl)-indole derivatives</u>

6-Methoxy-4-(3-pyridyl)-indole (91). This compound was prepared from **68** (580 mg, 3.03 mmol) and 3-bromopyridine (260 μL, 2.7 mmol) by the same procedure used for the synthesis of **88**. After column chromatography (silica, 2% MeOH in CH_2Cl_2), a pale yellow foam was obtained in 93% yield (562 mg). An analytical sample was crystallized

from EtOAc/hexane to give pale yellow needles: mp 108-109 °C; ^{1}H NMR ($CDCl_3$) δ 8.94 (d, 1, ArH, J = 1.8 Hz), 8.61 (dd, 1, ArH, J = 1.4 and 4.9 Hz), 8.24 (bs, 1, NH), 7.96 (ddd, 1, ArH, J = 1.4, 1.4 and 7.9 Hz), 7.39 (dd, 1, ArH, J = 5.0 and 7.8 Hz), 7.17 (dd, 1, ArH, J = 2.7 and 2.8 Hz), 6.93 (d, 1, ArH, J = 1.4 Hz), 6.86 (d, 1, ArH, J = 2.0 Hz), 6.58 (s, 1, ArH), 3.86 (s, 3, OCH_3); CIMS 225 (MH^+), Anal. ($C_{14}H_{12}N_2O$).

6-Methoxy-4-(3-pyridyl)-indol-3-ylglyoxylic acid (93). This compound was prepared in 57.8% yield from **92** (224 mg, 1 mmol) by the procedure used for the synthesis of the compound **90** as a yellow solid: mp 172-176 °C; ^{1}H NMR (DMSO-d_6) δ 12.01 (bs, 1, NH), 8.45-8.26 (m, 2, ArH), 8.15 (s, 1, ArH), 7.65 (dd, 1, ArH, J = 1.4 and 6.4 Hz), 7.31 (dd, 1, ArH, J = 4.7 and 8.9 Hz), 7.03 (d, 1, ArH, J = 2.2 Hz), 6.69 (d, 1, ArH, J = 2.0 Hz), 6.89 (s, 1, ArH), 3.85 (s, 3, OCH_3); FABMS 297 (MH^+).

2-Methoxyindolo[4,3-*fg*]-6-quinolone (94). A 50 mL of an aqueous solution containing $AgNO_3$ (17 mg, 0.1 mmol), $NH_4S_2O_8$ (690 mg, 3 mmol), and TFA (770 μL, 1 mmol) was prepared. Compound **93** (30 mg, 0.1 mmol) was added to 5 mL of the above solution with CH_2Cl_2 (5 mL). The reaction mixture was stirred for 5 h at 40 °C, basified with NH_4OH, and the layers were then separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the organic extract was washed with water (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. After column chromatography (silica, 5% EtOH in CH_2Cl_2), compounds **94** (6 mg, 24%) and **95**

(11 mg, 44%) were obtained both as a yellow solids: **94:** ^{1}H NMR (DMSO-d_6) δ 11.08 (bs, 1, NH), 8.73 (s, 1, ArH), 8.60 (d, ArH, J = 4.3 Hz), 7.96 (d, ArH, J = 8.1 Hz),7.47 (dd, 1, ArH, J = 4.7 and 7.8 Hz),6.59 (d, 1, ArH, J = 1.9 Hz), 6.42 (d, 1, ArH, J = 1.9 Hz), 3.85 (s, 3, OCH_3); CIMS251 (MH^+).

2-Methoxy-6-indolo [3,4-*fg*] isoquinolone (95). Isolated as described above: ^{1}H NMR (DMSO-d_6) δ 12.7 (bs, 1, NH), 9.82 (s, 1, ArH), 8.77 (d, 1, ArH, J = 5.1 Hz), 8.47 (s, 1, ArH), 8.14 (d, 1, ArH, J = 5.1 Hz), 7.94 (s, 1, ArH), 7.26 (d, 1, ArH, J = 1.3 Hz), 4.12 (s, 3, OCH_3).

Table 2. Elemental Analysis Data.

	%C	%C	%H	%H	%N	%N
	Cal'd	Found	Cal'd	Found	Cal'd	Found
19	60.85	60.56	5.84	5.81	10.14	10.15
33	60.78	60.90	5.64	5.48	3.73	3.73
41	63.36	63.37	5.65	5.37	4.62	4.59
47	63.49	63.39	5.89	5.80	3.90	3.87
28	50.89	50.76	3.20	2.90	4.95	4.88
51	57.38	57.39	6.65	6.53	3.19	3.19
65	46.50	46.78	3.55	3.54	4.93	4.60
67	47.82	48.18	3.57	3.51	6.20	6.22
75	65.02	65.29	4.46	4.70	6.89	6.61
76	42.99	43.13	2.41	2.24	4.18	4.11
91	74.98	74.66	5.39	5.37	12.49	12.38

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VITA

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